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EXPERIMENTAL STUDIES ON THE PATHOGENESIS AND TREATMENT OF OCULAR TUBERCULOSIS*

BY

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Inaugural Address at the Opening of the Institute of Ophthalmology, London

THE investigations which it is my privilege to summarize here have extended over a twelve-year period. Since the more recent studies on the action of antibiotics are as yet in press, it is an additional pleasure to present them here in England, the home of Fleming's and Florey's great and fundamental work, before their actual publication.

A number of my colleagues have participated in this work and are co-authors of the various reports. To these gentlemen I extend

* From the Wilmer Ophthalmological Institute of the Johns Hopkins University and Hospital. These studies were supported by grants from the John and Mary R. Markle Foundation. The technical details of these experiments and reviews of the pertinent literature are given in the various reports on "Experimental Studies in Ocular Tuberculosis" which have appeared or are in print in the Archives of Ophthalmology.

full acknowledgment for the major part they have played in these investigations.

These studies were primarily stimulated by Rich's demonstration in 1929 of the independence of hypersensitivity and immunity, and his explanation then given of the pathogenesis of the tubercular lesion. Prior to Rich's contribution, it was generally supposed that the phenomena of hypersensitivity and immunity were interdependent. Since the time of Koch, it had been clearly recognized that, to comparable doses of the tubercle bacillus, the normal animal reacts in a manner quite different from the animal previously infected with tuberculosis. When the normal animal is infected by the local injection of living bacilli, there is an insignificant reaction at the site of the injection. Thereafter there ensues a slow propagation of the bacilli, involvement of the regional lymph nodes and the formation of hard tubercles. As the infection progresses beyond the local lymph nodes, there follows a widespread systemic infection, first with hard tubercles, which may either become fibrosed, or else necrotic, caseous, and softened. On the other hand, when the previously tuberculous animal receives a comparable injection of bacilli, a sharp inflammatory reaction occurs at the site of the injection. This is characterized clinically by oedema, erythema, induration, and sometimes even by necrosis and sloughing. Histologically this reaction is characterized by a primary outpouring of serum and leucocytes, and later a mobilization of macrophagic cells. The bacilli tend to become fixed at the site of the injection, and, if the infecting dose were small, they may even be destroyed.

The natural deduction from this observation was that the initial inflammatory reaction, which was correctly interpreted as a hypersensitive phenomenon, was intimately related, or indeed responsible for, the local fixation and destruction of the bacilli. In other words, allergy was responsible for immunity. This idea Rich challenged in 1929, pointing out that while this dictum was widely accepted, there was no scintilla of experimental evidence to support it. In a series of brilliant experiments, he and his co-workers demonstrated that there was no relation between hypersentivity and resistance, and that the previously tuberculous animal could be completely desensitized to the extent that not only the soluble bacterial products, but even living bacilli injected in the skin, caused no local inflammatory reaction. At the same time the resistance to dissemination of the bacilli, or immunity to reinfection, was totally undisturbed. As a result of these and other investigations, Rich stated that the factors governing the development and course of a tuberculous lesion could be expressed in an equation, now known as Rich's law. This equation is :—

$$\text{Lesion} \propto \frac{\text{No. and virulence of bacilli} \times \text{Allergy}}{\text{Resistance}}$$

Thus following infection with a moderate or large dose of virulent bacilli, if there is a high tissue allergy and a low immunity, an inflammatory, caseating, necrotizing lesion results. On the other extreme, if the number of infecting bacilli is small, and if there is a low degree of tissue allergy and a high resistance, there will be little inflammation or tissue destruction. Rapid encapsulation and healing occur, and there may even be complete destruction of the bacilli. Varying degrees of infection, allergy and resistance, between these two extremes, explain the various intermediate types of the tubercular lesion.

This concept of the pathogenesis of a tubercular lesion offered obvious therapeutic points of attack. These were, first, an enhancement of resistance which had long been the cornerstone in the treatment of tuberculosis. The second point of attack would be the removal of the fatal tissue allergy, or desensitization. This was something of a new idea, tuberculin previously having been used somewhat disastrously and fruitlessly on the old peri-focal concept, *i.e.*, that since hypersensitivity was assumed to be responsible for immunity, hypersensitive reactions should be encouraged. Thus tuberculin therapy fell somewhat into disrepute. The third point would be a direct attack on the tubercle bacilli, a therapeutic measure which up to that time had been unsuccessful, there being no chemo-therapeutic or antibiotic agent yet demonstrated with any real deterrent action on the tubercle bacillus.

It was the purpose of the investigations which I summarize today to investigate experimentally first, the validity for ocular tuberculosis of Rich's law, and secondly, the therapeutic possibilities suggested thereby.

At the beginning of these studies, there was already considerable reason to believe that Rich's law, or some modification thereof, governed the lesions of tuberculosis in the eye. Primarily, it had been known for some years that experimental ocular tuberculosis ran quite a different course in the normal animal and in the animal previously infected with tuberculosis (the immune-allergic animal). This had been clearly shown as early as 1924 by Henri Lagrange. Secondly, the most striking characteristic of clinical ocular tuberculosis is its amazing pleomorphism. Certainly some extrinsic factors are responsible for the widely varying manifestations of the disease in the eye. The obvious factors are those enumerated by Rich—the dose and virulence of the infecting organism, the degree of tissue allergy present, and the degree of

systemic immunity to infection. It was not known, however, to what extent these factors would be effective on a localized tuberculous lesion in the tightly enclosed scleral and corneal envelope. One troublesome point in the acceptance of this law for ocular tuberculosis was the clear fact that certain experimental animals and humans with ocular tuberculosis showed a high degree of acute inflammation and even caseation in the eye, indicating a high degree of local tissue hypersensitivity, while the cutaneous reactivity of these animals and humans to tuberculin was low or absent.

The immediate objectives of these investigations may therefore be listed as follows:—

I. *Pathogenesis.* Does Rich's law for the pathogenesis of the tuberculous lesion hold true in localized ocular tuberculosis? This was explored by determining: A. The effect of the number and virulence of the infecting organism on the resulting ocular lesion. B. The influence of local tissue sensitivity. C. The influence of systemic immunity. D. The relation of cutaneous and ocular sensitivity.

II. *Therapy.* A. Is enhancement of local resistance or immunity possible? B. What is the effect of desensitization on the local ocular lesion? C. What are the possibilities of sulfone and antibiotic treatment in ocular tuberculosis?

This was an over-ambitious programme. On some points, notably the stimulation of an artificial local immunity, we have not even scratched the surface. On other points, while the work is incomplete and fragmentary, some information has been adduced which confirms the validity of Rich's law on the pathogenesis of the tuberculous lesion in the eye, and strengthens the suggestions for therapy. Some observations have been made on the therapy of experimental ocular tuberculosis which appear to have a bearing on the clinical attack on the disease. These experiments may be summarized as follows:—

THE PATHOGENESIS OF OCULAR TUBERCULOSIS

A. *The influence of the number and virulence of organisms.* The first problem was the determination of the proper strain of tubercle bacilli to be used in the experimental animals and the proper dosage. This was largely a trial-and-error procedure, and it is unnecessary here to go into the various details. Suffice to say that avian and bovine strains proved unsuitable for use in the rabbit on account of the malignant course of the ocular disease

when the organisms were injected into the eye, and the speedy death of the rabbits from generalized tuberculosis when the organisms were injected systemically. A virulent human strain was finally used. Injected into the eye of a normal or immune-allergic rabbit in proper dose, satisfactory lesions developed, and injected systemically, the animals rarely developed widespread tuberculosis, but as a rule developed a self-limiting disease with inconspicuous histological findings, from which they recovered spontaneously, retaining a well developed hypersensitivity to tuberculin, and a definite acquired resistance to re-inoculation—an immune-allergic status. The ocular inoculations were all made in the anterior chamber. Intra-carotid inoculations were unsatisfactory for such a prolonged study as this, because the development of ocular tuberculosis in such animals was a chance and inconstant affair.

When a small dose of the bacilli was injected into the anterior chamber of a normal rabbit, there was a minimal or no local reaction to the injection. About the fourteenth day after injection, these rabbits developed slight peri-corneal injection, slight steaminess of the cornea, and hard tubercles over the iris. About the fourth week this indolent reaction became aggravated, vascularization of the cornea became evident, and acute inflammation, and later, evidences of necrosis and caseation developed. About the sixth week, or thereafter, some of the eyes perforated. In the remainder, beginning about the eighth or tenth week, the acute inflammation began to subside, and the eyes entered the stage of beginning fibrosis. By the twenty-third or twenty-fourth week the disease was usually inactive, leaving blind, scarred and sometimes perforated eyes (Study 2).

When a larger dose of the same virulent organisms was given, this picture was greatly accelerated, the degree of acceleration depending upon the amount of bacilli present in the inoculum. The incubation period before the development of symptoms was shortened to a week or less, the acute inflammatory phase developed rapidly, and perforation of the eyes within four to six weeks was the general rule.

When the eyes of normal rabbits were inoculated with a attenuated strain of human organisms, the results were minimal. The inflammatory symptoms were slow in appearance, and of low degree. Many eyes showed little or no reaction, and those that did show disease usually healed within three months with minimal damage and scarring.

In the immune-allergic rabbit—the animal recovered from a previous systemic infection—the course of the ocular disease after

anterior chamber inoculation was quite different. Primarily in order to produce any tuberculous disease in the eyes of these rabbits, it was found necessary to give a much larger dose of the same virulent bacilli, the minimum dose required to produce low grade tuberculous disease in the eyes of these rabbits being usually fifty times that required for the normal rabbit. When this dose was given in the anterior chamber, there developed within 24 hours a marked inflammatory reaction which subsided within a few days. This was similar to the reaction caused by the anterior chamber injection of tuberculin, and was obviously a reaction to the tuberculo-protein in the inoculum, the eyes, like the other body tissues, having become sensitized by the prior systemic infection. After the subsidence of this tuberculin reaction, the eyes remained asymptomatic for a period of two weeks or longer. Then low-grade ciliary congestion developed, and sometimes discrete tubercles appeared in the cornea and iris. Thereafter the eyes ran a restrained course of chronic inflammation, showing moderate secondary iridic and corneal changes with vascularization. The inflammatory reaction slowly increased, reached a low maximum about the fourth week, continued to the tenth or fourteenth week, and then gradually subsided. The maximum degree of inflammation resulting from the minimal dose capable of producing lesions was decidedly less than that eventually developing in the eyes of the normal rabbits affected with their minimal dose, and perforation practically never occurred (Study IV). In fact, the course of the disease in its various corneal and iris manifestations simulated amazingly ocular tuberculosis in the human adult.

If a larger dose of the virulent bacilli was given to the immune-allergic rabbits, the entire picture was reversed. There was an early violent reaction which never subsided, the eyes rapidly developed a spreading destructive inflammation, with necrosis and caseation, and there was a high percentage of rupture within 6 weeks. The process was even more acute and destructive than the disease in the normal rabbit (Study VI).

When avirulent organisms were given to immune-allergic rabbits, local tuberculous disease did not result, and there was no reaction other than the immediate one to the tuberculo-protein in the inoculum.

From the experiments, it is clearly apparent that the importance of the dose and virulence of the infecting organisms holds true in ocular tuberculosis. In the normal animal with a minimal dose of virulent bacilli, there is a slowly spreading infection, which becomes acute as the organisms propagate and spread through the eye. With a larger dose of the same organisms this reaction is violently accelerated. With avirulent organisms there is little

or no reaction. In the immune-allergic animal, where the propagation and spread of the organisms is restrained by the acquired systemic resistance, after the reaction to tuberculo-protein subsides, the subsequent inflammation is of low degree, and parallels the slow propagation of the bacilli in the eye. However, with a larger dose of bacilli, there is a violent immediate inflammatory reaction, the immunity is overwhelmed, the bacilli propagate rapidly, and necrosis, caseation and rupture occur early.

In the subsequent experiments, in both the normal and immune-allergic rabbit, the minimum dose capable of producing lesions with fair constancy, was uniformly used.

B. *The influence of hypersensitivity on the ocular lesion.* It has already been noted that acute inflammation with necrosis and caseation develops in the normal rabbit as the bacilli propagate and spread through the eye. In the immune-allergic rabbit after the immediate hypersensitive reaction subsides, acute inflammation develops only as the bacilli propagate, is of lower degree than in the normal, and there is minimal necrosis and caseation. What is the relation of this acute inflammation to hypersensitivity of the eye?

The ocular sensitivity can be accurately gauged by the injection of tuberculin* into the anterior chamber, estimating the clinical reaction, and then enucleating these eyes and evaluating the histological reaction. This was done at weekly intervals in sample pairs of rabbits throughout the course of several experiments. Thus a graph could be prepared illustrating the development and the course of ocular sensitivity during any period of observation. Likewise, by clinical estimation on a numerical scale, the degree of ocular inflammation resulting from infection could be estimated in the remaining animals of the group, graphed, and compared with the degree of ocular hypersensitivity as measured by the intra-ocular tuberculin test in the sample rabbits. This was done for both normal rabbits (Study II) and for immune-allergic rabbits (Study IV). The validity of graphs was checked statistically (Study IV).

The results of this graphic study for normal rabbits are shown in Fig. 1, and for immune-allergic rabbits in Fig. 2. The ordinates represent the degree of ocular inflammation and sensitivity and the abscissae the time in weeks. Thus it is evident that in both the normal and immune-allergic animals with ocular tuberculosis, the degree of ocular inflammation resulting from infection closely parallels the degree of ocular sensitivity. The ocular inflammation

* The tuberculin used for the determination of ocular sensitivity was the purified protein derivative of Seibert, known as P.P.D.

resulting from infection increases as the degree of ocular reactivity to tuberculin (P.P.D.) increases, and in general decreases as this ocular reactivity wanes.

The influence of sensitivity on the ocular lesion was further investigated in two other experiments. In the first experiment, advantage was taken of the fact that when rabbits are inoculated

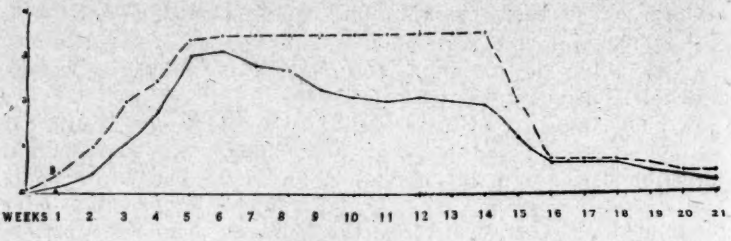


FIG. 1.

Curves showing the relation of ocular inflammation to ocular sensitivity. Curve A represents the ocular inflammation and curve B the ocular sensitivity.

systemically with virulent human tubercle bacilli, they do not all develop a uniform amount of allergy. Thus by initially using a large number of rabbits, when the appropriate period has elapsed after systemic inoculation, certain individual animals showing marked cutaneous hypersensitivity and others showing a low

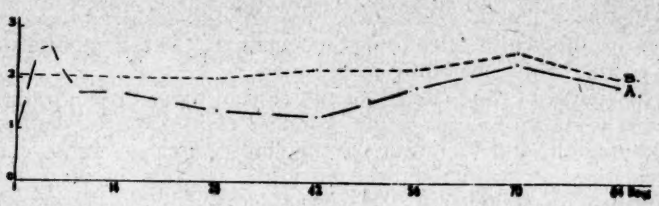
FIG. 2.

Relation of ocular sensitivity (A) to ocular activity (B) after intraocular injection of tubercle bacilli in immune-allergic rabbits.

degree of cutaneous hypersensitivity can be selected. As will later be pointed out, in immune-allergic rabbits without ocular disease, the ocular sensitivity parallels the cutaneous sensitivity. Thus two sets of rabbits, one with high ocular and cutaneous sensitivity, and the other with low ocular and cutaneous sensitivity, were made available for inoculations of the eye and study of the resulting inflammation. During the progress of this experiment,

specimen pairs of animals were sacrificed at weekly intervals to determine the course of the ocular sensitivity.

Fig. 3 shows the course of the ocular inflammation and ocular sensitivity in the rabbits with initial high sensitivity, the ordinates again representing the degree of ocular sensitivity and inflammation, and the abscissae the time in days. Thus it is apparent that



A. Ocular Inflammation.
B. Ocular Sensitivity.

FIG. 3.

Course of ocular activity and of ocular sensitivity in rabbits with initial high cutaneous sensitivity. A, ocular activity, and B, ocular sensitivity.

A. Ocular Inflammation.
B. Ocular Sensitivity

FIG. 4.

Course of ocular activity and ocular sensitivity in rabbits with initial low cutaneous sensitivity. A, ocular activity, and B, ocular sensitivity.

rabbits with a high degree of sensitivity showed an immediate high degree of reaction to the tuberculo-protein in the inoculum, and a high degree of persisting ocular inflammation. Again the degree of ocular inflammation resulting from the infection paralleled the degree of ocular sensitivity to tuberculin.

Fig. 4 shows the same findings in rabbits with an initial low sensitivity. The primary reaction to the tuberculo-protein in the inoculum was low, and the early inflammatory symptoms slight. However, as the bacilli spread slowly through the eye, the ocular sensitivity to tuberculin increased, and ocular inflammation

resulting from the infection likewise increased and paralleled the ocular sensitivity to tuberculin.

In the second experiment (Study VI), a group of immune-allergic rabbits was divided into three sub-groups A, A^1, and B. Prior to inoculation of the eyes, the A rabbits were desensitized with tuberculin, and in order to maintain desensitization, the tuberculin treatment was continued after the anterior chamber inoculation. The A^1 rabbits were partially desensitized, and were given no tuberculin after ocular inoculation. The B rabbits were not treated with tuberculin at any time.

The course of the ocular inflammation in these three groups of rabbits is shown in Fig. 5, the ordinates expressing the degree of inflammation, and the abscissae the elapsed time in weeks. The desensitized A rabbits showed no initial reaction in the eyes to the tuberculo-protein in the inoculum, and later developed a

FIG. 5.

Average ocular activity of reacting rabbits of groups A, A^1 and B.

restrained ocular tuberculosis of low degree. Only at the end of the eighteenth week, when the disease was beginning to subside in all three groups, did the clinical inflammation of the desensitized A rabbits approximate that of the other two groups. On the other hand, both the partially desensitized A^1 rabbits, and the hypersensitive B rabbits showed a marked degree of reaction to the tuberculo-protein in the inoculum, and both groups showed more severe inflammatory reactions in the eyes than did the desensitized rabbits.

Thus it appears that the influence of tissue allergy on the resulting tuberculous lesion is substantiated for ocular tuberculosis. In both normal and immune-allergic rabbits, infected in the eye with the minimal dose of bacilli capable of producing constant symptoms, the ocular inflammation, necrosis and caseation, parallel the degree of ocular sensitivity. In immune-allergic rabbits with an initial high ocular sensitivity, the immediate ocular inflammation is severe, and so remains. In similar rabbits with an initial low ocular sensitivity, the ocular inflammation is low at first, and only develops as the ocular sensitivity increases. Desensitization prior to inoculation abolishes the primary ocular reaction to

tuberculo-protein, and the ocular inflammation resulting from inoculation of the eyes is of low degree when the desensitized status is maintained.

C. *The influence of immunity on the ocular lesion.* The degree of immunity existing in the various immune-allergic animals was not uniformly quantitated by the injection of living bacilli in the skin, and clinical and histological examination of the resulting reaction. In the early experiments this was done in a number of rabbits, but no noteworthy differences in the reaction were observed, and the procedure introduced the element of possible changes produced by a second infection. The information on the rôle of immunity on the ocular lesion, as evidenced by these experiments, may be summarized as follows.

First, the minimal dose of bacilli which produces marked ocular disease in the normal rabbit, has no effect when introduced in the eye of a rabbit recovered from a prior systemic infection (Study III). The rabbit has developed a resistance to re-inoculation. Second, it requires approximately fifty times this dose to produce tuberculous disease in the eyes of immune-allergic rabbits, the amount varying in different animals. In a small percentage of immune-allergic rabbits, no ocular disease resulted from the standard fifty-fold dose. Third, this resistance to re-inoculation is only relative. If enormous doses are given, it is immediately overwhelmed, and violent inflammatory symptoms develop (Study VI). Fourth, this resistance to re-inoculation is totally undisturbed by complete desensitization of the rabbits prior to inoculation (Study VI). It still requires the same increased dose to produce ocular lesions, as compared with the normal rabbit. In fact, in this experiment, the desensitization appeared actually to favour the action of the immunity, the desensitized group showing a slightly higher incidence of complete immunity, and a decided increase in the incubation period—seven weeks as compared to two weeks in the sensitive controls.

There is therefore considerable confirmation for the influence of immunity on the tuberculous lesion in the eye. The course of the ocular disease is radically different in normal animals with no immunity, and in immune-allergic animals with immunity from a prior infection. While the degree of immunity resulting from a prior infection may be variable, it always requires a much higher dose of bacilli to produce tuberculous lesions in the previously infected animal than it does in the normal animal. Immunity functions entirely independently of sensitivity, and indeed in these experiments appeared somewhat enhanced when sensitivity was removed.

D. There remains one last point to be discussed in this connection—the puzzling question of why certain experimental animals, and likewise clinical patients with ocular tuberculosis, show a low degree of cutaneous reactivity to tuberculin, when the clinical appearance of the eye would indicate a high degree of tissue sensitivity.

This was investigated by simultaneous estimations of the cutaneous and ocular reactivity to tuberculin (*a*) in systemically infected animals without ocular disease, (*b*) in normal animals infected with tubercle bacilli in the eye, and (*c*) in immune-allergic animals secondarily infected in the eye.

Fig. 6 illustrates the general parallelism between ocular and cutaneous sensitivity in systematically infected animals without ocular disease (Study I). While there were wide fluctuations, in

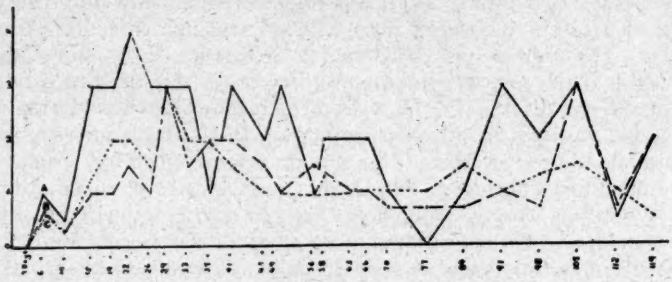


FIG. 6.

Curves showing the parallelism of ocular and cutaneous sensitivity in the systemically infected rabbits. Curve A represents the cutaneous sensitivity; curve B the clinical ocular sensitivity, and curve C the histological ocular sensitivity.

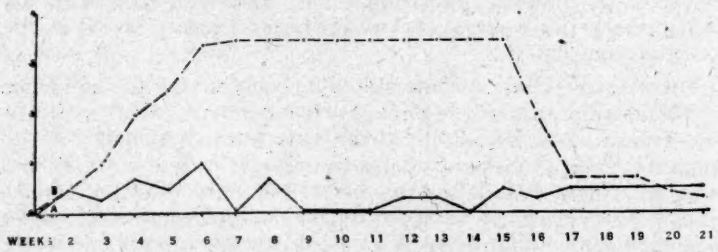


FIG. 7.

Curves showing the relation of the ocular sensitivity to cutaneous sensitivity in the normal rabbit after inoculation of the anterior chamber with tubercle bacilli. Curve A represents the cutaneous sensitivity, and curve B the ocular sensitivity.

general the cutaneous and ocular sensitivity paralleled each other. The most marked fluctuations occurred in the cutaneous sensitivity, when hot weather appeared to increase the cutaneous reactivity.

Fig. 7 represents the relation of ocular reactivity to tuberculin to cutaneous sensitivity in normal animals inoculated in the eye with tubercle bacilli (Study III). As the bacilli propagate and spread through the eye, intense local reactivity to tuberculin develops which only subsides when the process burns out. The cutaneous reactivity to tuberculin is only slightly stimulated by the local disease process in the eye. In short, in the otherwise

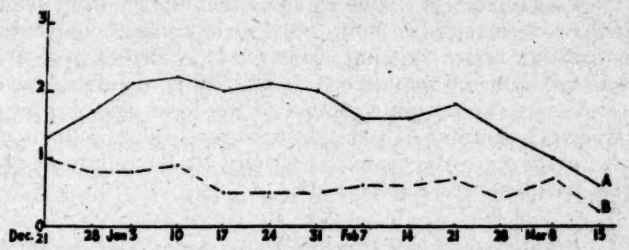


FIG. 8.

(Experiment 1)—Relation of ocular sensitivity (A) and cutaneous sensitivity (B) after intra-ocular injection of tubercle bacilli in immune-allergic rabbits.

normal animal with local ocular tuberculosis, the cutaneous reactivity to tuberculin is no index of the ocular reactivity.

Fig. 8 shows the relative ocular and cutaneous reactivity to tuberculin in immune-allergic rabbits infected in the eye with tubercle bacilli (Study IV). At the time of inoculation the ocular and cutaneous sensitivity were about the same, as would be expected. As the bacilli spread slowly throughout the eye, there was a concomitant slow rise in the local ocular reactivity or sensitivity. The ocular sensitivity began to decline slowly at the end of the ninth week, as the local disease subsided. The cutaneous sensitivity, however, was not affected by the local ocular disease, and over a three-month period slowly declined and faded.

These experiments offer an explanation for the relative cutaneous anergy sometimes observed in ocular tuberculosis with acute inflammation. If there is local tuberculous disease in the eye there is no necessary relation between the ocular reaction to the products of the tubercle bacillus and the cutaneous sensitivity. If the cutaneous sensitivity is high, the ocular sensitivity is also high,

for the eye partakes of the general systemic sensitivity. However, local disease in the eye may produce a high degree of ocular sensitivity to tuberculin, while it does not influence or affect a normally low cutaneous sensitivity. In other words, if the cutaneous sensitivity is low, it does not necessarily imply that the ocular sensitivity is also low. The latter may be high or low, depending on the presence and extent of an ocular tuberculosis. Whether the increased ocular reactivity to tuberculin is the result of an increased vascularity produced by the local disease, or is a true selective local sensitization, is largely an academic question which need not concern us here.

It seems reasonable to conclude from these experiments that the principles involved in Rich's law, laid down for systemic tuberculous lesions, also hold good in localized ocular tuberculosis without active systemic lesions. It is further evident that the determination of the cutaneous reactivity to tuberculin does not always give an accurate picture of the local ocular reactivity. If cutaneous sensitivity is low or absent, and there is tuberculous disease in the eye, the ocular reactivity to the products of the tubercle bacillus may still be high.

II.—The Treatment of Experimental Ocular Tuberculosis

A. *The Enhancement of Immunity.* In 1893 Trudeau stated that the achievement of a complete artificial immunity in tuberculosis was an ideal never likely to be attained. Unfortunately that is still largely true today. It has already been pointed out that as a result of a prior infection, the rabbit acquires a well marked resistance to re-inoculation. This well known fact has been employed in the mass inoculation of children with the attenuated B.C.G. organism, and the results have been somewhat gratifying in the lessened incidence of tuberculosis in the inoculated group. This lengthy procedure is, however, a far cry from the artificial stimulation of an immunity calculated to benefit an already existing infection. While we have done little work on this problem, and the little we have done has been quite barren of any results, one observation has been made which may be of some academic interest.

It was noticed that in immune-allergic rabbits with a secondary ocular tuberculosis, the clinical evidences of inflammation and activity might entirely subside while there was still a low degree of demonstrable sensitivity in the affected eye, and that these eyes did not develop further tuberculous disease when given a second injection of bacilli shortly after the subsidence of symptoms (Study VI). It was thought at first that this might be due to an exhaustion

of the reactive capacity of the eye, but this supposition was proven untrue, since the eyes reacted quite briskly to other non-tuberculous stimuli and infections. It was then supposed that this phenomenon might be due to an increase in the general immunity brought about by the recent ocular disease from which the animal had recovered. This supposition was also untenable, because it was found that the second undiseased eyes of these same rabbits reacted quite promptly to the injection of the proper dose of bacilli (Study VI). Another possible explanation was that this healing and immunity to re-inoculation might be due to the increased vascularity produced by the ocular disease, thus rendering the humoral element of the general immunity more efficacious. Experiments (Study VIII) in immune-allergic rabbits with eyes vascularized by other non-tuberculous infections, revealed that increased vascularity was not in itself the dominant factor in this resistant state, and indicated some mechanism other than humoral immunity.

Continued study of these apparently immune eyes revealed the fact that the local immunity was only transitory, that spontaneous recurrences of the inflammation occurred in 25 per cent. of such rabbits within a year, and within this same time the remaining 75 per cent. lost their immunity, and these eyes developed a further attack of ocular tuberculosis on re-inoculation (Study VIII). Further, the histological examination of eyes recently recovered from an attack of tuberculosis, and presumably immune to re-inoculation, revealed definite sub-clinical areas of infection with epithelioid cells and macrophages. Examination of similar eyes a year later, when they were again theoretically susceptible to re-inoculation, showed that the epithelioid cells and macrophages had largely disappeared.

On the basis of these observations it was concluded that the transient immunity to re-inoculation shown by eyes recently clinically recovered from tuberculosis was due not to a humoral immunity, but to the persisting mobilization of macrophagic cells. In short, whatever might be the rôle of the circulating anti-bodies in immobilizing and fixing the bacilli, the *sine qua non* in this local resistant state appeared to be the presence of macrophagic cells.

The obvious method of testing this hypothesis was the premobilization of macrophagic cells in the eye prior to the introduction of the infecting bacilli. This we attempted to do by the local injection of tuberculo-phosphatides in the anterior chamber, and finally in the stroma of the ciliary body.

This experiment, previously unreported, was completely inconclusive. When phosphatides were introduced into the anterior

chamber, they were apparently immediately excreted, and the eyes on section showed no cellular response. When the phosphatide was injected in the ciliary stroma, there ensued a clinical inflammatory reaction, and histologically an outpouring of epithelioid cells and macrophages. When such eyes were later injected with tubercle bacilli and compared with controls, it was difficult to differentiate with any certainty the tuberculoid lesions caused by the phosphatides and true tubercular lesions produced by the living bacilli. The intra-ocular injection of phosphatides did not appear to be a happy experimental approach to the problem. Thus these efforts to enhance the local resistant state have been fruitless.

B. *The Effect of Desensitization on Experimental Ocular Tuberculosis.* Prior to Rich's paper in 1929, it was generally supposed that allergy and immunity were inter-dependent, and that by evoking an allergic reaction, immunity might be stimulated. This was the idea underlying the therapeutic use of tuberculin in localized tuberculosis—namely to evoke sub-clinical allergic reactions and thus stimulate immunity. This was known as the perifocal concept. Rich's demonstration of the independence of allergy and immunity introduced at once the new therapeutic concept of removing the fatal tissue hypersensitivity by desensitization with tuberculin. Thus tuberculin would be given sub-cutaneously with the idea of avoiding all clinical or sub-clinical focal reactions, and the dose would be increased only as the point of reactivity receded. By this means tissue desensitization would be finally accomplished. However, it is quite true that either clinical or sub-clinical reactions will produce some desensitization, in that they deplete the local antibody reservoir. The value of avoiding focal reactions is therefore to obviate the local destructive effect such focal reactions necessarily entail.

In experimental work with rabbits, it is impracticable to employ the long-drawn-out process of desensitization with the small doses of tuberculin one would use in humans. Rabbits are not the happiest animals to use for desensitization experiments with tuberculin. They do not become hypersensitive as readily as guinea-pigs, they tolerate huge doses of tuberculin somewhat better than guinea-pigs and vastly better than humans. Lastly, since the ocular disease naturally runs a self-limiting course of from three to six months, it is necessary to accomplish desensitization rapidly in order to evaluate any observed therapeutic results. In the experiment to test the effect of desensitization on an already existing ocular tuberculosis in the immune-allergic rabbit, tuberculin was therefore administered subcutaneously in the large dose of 100 mgms., or (0·1 c.c.) of old tuberculin twice weekly. While a

focal reaction was observed following the first dose, this reaction was evanescent and did not produce any ocular damage. That this focal reaction was not responsible for the therapeutic effect was demonstrated by the observation that a precisely similar focal reaction had no effect on the hypersensitive controls which were not maintained in a state of desensitization.

The essence of this experiment (Study VII) was to prepare a large series of immune-allergic rabbits with secondary ocular tuberculosis. As soon as the ocular disease was established clinically, the rabbits were divided into two groups of equal severity. One group was untreated, while the second group was treated with tuberculin. The clinical course of the two groups was followed, and various minor tests were made during the course of the experiment to determine the progress of desensitization.

The results of this experiment are shown graphically in Fig. 9. After the inoculation of the eyes with tubercle bacilli there was an immediate reaction in the eyes to the tuberculo-protein in the inoculum. This rapidly subsided, and well-marked tuberculous lesions in the eyes were present by the third week, when the rabbits were divided into two groups of equal severity. Tuberculin was then started in one group. There was an immediate focal reaction in the eyes which subsided within one week. Thereafter the severity of the disease in the treated group, which continued to receive the desensitizing injections, rapidly subsided as compared with the untreated group, and at the end of the twelfth week, this difference in the two groups was marked. As the experiment progressed to the twenty-fourth week and the ocular disease in the control group naturally burned out, the picture in the two groups approximated each other. Various minor tests, the determination of ocular reactivity in the control group, the determination of the relative ocular sensitivity of sample pairs from the two series, the estimation of the ocular and cutaneous sensitivity at the end of the experiment, all indicated that the observed clinical improvement in the treated group paralleled their desensitization to tuberculin. Indeed, there was some evidence that there was a selective desensitization of the eyes, which might be expected, since it is known that tuberculin is a fine colloid and tends to filter out at the site of local inflammation.

The ultimate fate of the desensitized rabbits is interesting, and may be of importance in planning the method in which tuberculin should be used clinically. At the completion of the experiment the treated rabbits showed a degree of cutaneous sensitivity so low that the animals were practically insensitive. One year later, after cessation of treatment, the sensitivity had returned, and the animals showed a high degree of both ocular and cutaneous sensitivity.

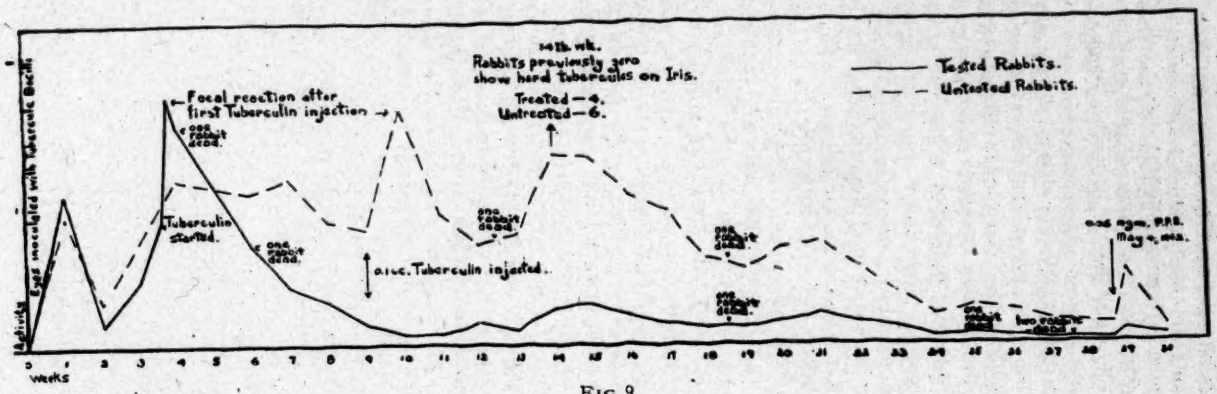


FIG. 9.

Effect of treatment on ocular tuberculosis in immune-allergic rabbits.

Synchronous with the return in sensitivity, there had been a disastrous ocular recurrence in 36 per cent. of the rabbits.

The conclusions to be drawn from this experiment appear clear. Desensitization with tuberculin is accompanied by a marked decrease in the clinical inflammatory manifestations of the disease, and exerts a thoroughly beneficial effect. It does not cure the disease in the sense of destruction of the bacilli, or even of bacteriostasis. It merely removes the factor responsible for the destructive phases of the lesion. If tuberculin treatment is terminated, the fatal tissue sensitivity recurs, and coincident with its return in a large percentage of the animals, there is a recurrence of the ocular inflammation.

C. *The effect of chemotherapy and antibiotics in ocular tuberculosis.* Prior to 1940, no therapeutic agent had been found with any marked specific deterrent action on the tubercle bacillus. It is true that Koch had observed the inhibitory action of colloid of gold salts on the *in vitro* growth of tubercle bacilli, but their clinical use had given no spectacular results, and the untoward effects were so severe that their use has been almost completely abandoned. Efforts had been made to treat tuberculosis with various dyes combined with metallic salts of bactericidal action. The thought behind such treatment was the known ability of such dyes to penetrate tubercles. The clinical results were, however, not encouraging. Some hope was later aroused by the demonstration that sulphanilamide used prior to inoculation had an inhibitory effect on the later development of tuberculosis in guinea-pigs. However, sulphanilamide had no effect in tuberculosis when used clinically. It was not until 1940, when Feldman and his co-workers showed the deterrent action of certain diamino-diphenyl sulphones in experimental tuberculous lesions, that there was any real demonstration of an effective chemo-therapeutic agent in tuberculosis. These sulphones were known as diasone, promin and promizole. Diasone was relatively toxic and therefore of little value. Promin was moderately toxic, while promizole was relatively non-toxic. In fact, promizole can be administered to humans up to 12-15 grams daily with comparative safety.

The first step in the study of chemo-therapy of ocular tuberculosis was to determine the effects of promin and promizole in both normal and immune-allergic rabbits with ocular tuberculosis. The drugs were administered in food in 1·0 per cent. concentration over a four-month period. The daily dose was approximately 1·5 gm., which produced a blood level ranging around 2·0 mgm. per cent. The results of this treatment in normal rabbits (Study XI) are shown in Fig. 10, where the course of the disease in the treated animals is compared with untreated controls. There was

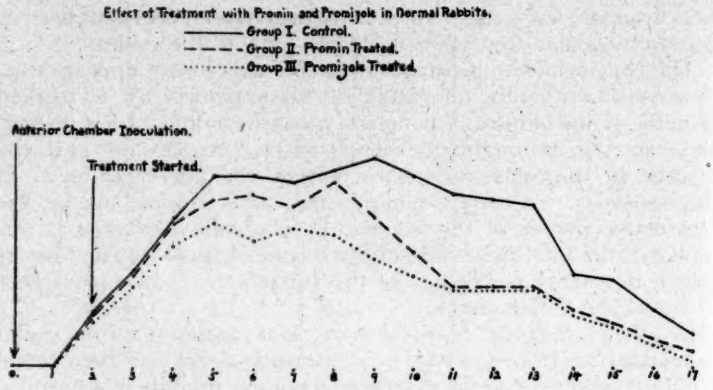

Effect of Treatment with Promin and Promizole in Normal Rabbits.
Group I. Control.
Group II. Promin Treated.
Group III. Promizole Treated.
Anterior Chamber Inoculation.
Treatment Started.

FIG. 10.

Effect of treatment with promin and promizole in normal rabbits.

a slight, but statistically insignificant, relative decrease in the disease in the treated animals at the end of the second week, and a slightly more significant decrease at the end of the eighth week. However, at the end of the twelfth week, the majority of the eyes in both the control and treated groups had gone into buphthalmos and ruptured. There was only a slight advantage in favour of the treated groups. There was little difference in the histological picture, and on transmission experiments from the diseased eyes the uveal tracts of both the treated and untreated groups were all infectious. It was concluded therefore that promin and promizole had only a very slight deterrent action on ocular tuberculosis in the normal animal.

The results of treatment in immune-allergic rabbits were much more striking. These results are shown in Fig. 11. After three

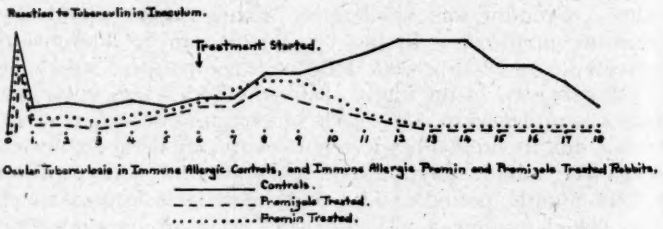

Reaction to Tuberculin in Inoculum.
Treatment Started.
Course of Ocular Tuberculosis in Immune Allergic Controls, and Immune Allergic Promin and Promizole Treated Rabbits.
Controls.
Promizole Treated.
Promin Treated.

FIG. 11.

Course of ocular tuberculosis in immune-allergic controls and immune-allergic promin and promizole treated rabbits.

weeks' treatment, the treated animals began to improve, while the disease became more severe in the untreated controls. At the end of the fourteenth week, when the disease in the controls was at its maximum, the eyes of the treated rabbits were almost completely inactive. At the end of the sixteenth week, the eyes of all the treated animals were entirely quiet on clinical examination, while 80 per cent. of the controls still showed active inflammation. The histological examination, however, was not so conclusive. Of the treated rabbits sacrificed for histological study, approximately 50 per cent. showed small, persisting areas of active tuberculosis, while the remainder showed only scarring. There was no statistical difference between the promin- and the promizole-treated animals. On transmission experiments, under the technique used in this experiment, only one of the treated animals showed an infectious uveal tract, while all the controls were positive.

It was concluded from this experiment that both promin and promizole had a marked deterrent action on ocular tuberculosis in the immune-allergic rabbit, but this action was not absolute in the sense of producing a complete destruction of the tubercle bacilli. In the light of the negative experiment in normal rabbits it was suggested that this deterrent action might be due either to a degradation or attenuation of the virulence of the organisms, allowing the resistance of the host to become more active, or to a partial bacteriocidal action, bringing the infection within the range of the host's resistance.

The next step in the search for agents with a deterrent action on the lesions of ocular tuberculosis was obviously to explore the effect of the antibiotics. Although Abraham, Chase and Florey had reported as a result of their *in vitro* experiments that the tubercle bacillus was insensitive to penicillin, nevertheless the literature was singularly barren of conclusive evidence that this was true *in vivo*. Such experiments as were reported were all open to the criticisms that the dosage was insufficient, or the number of animals too few to validate any conclusion. It seemed, therefore, worth-while to investigate the question further.

Normal rabbits, injected in the eye by the usual anterior chamber injection, were used (Study IX). This was admittedly a severe test. Sixteen rabbits were treated with penicillin, 200,000 units per diem, in divided doses, for a period of 45 days. An equal number of similarly infected, but untreated, rabbits served as controls. The results of this experiment are shown in Fig. 12. The clinical course of the treated and untreated rabbits was identical. Penicillin had no effect whatsoever on the clinical lesions. Histological examination of the treated and untreated eyes showed slightly less tuberculous disease in the treated eyes,

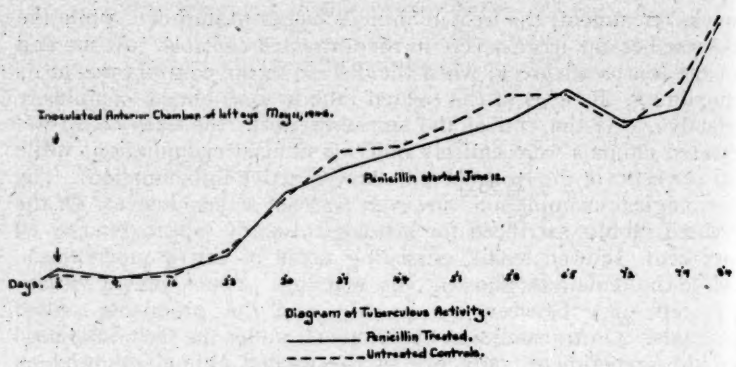


FIG. 12.

Diagram of tuberculous activity in controls and penicillin treated rabbits.

but when this was subjected to statistical analysis it was found to be without significance. It was concluded that penicillin was without action in ocular tuberculosis under the conditions of this experiment.

The last experiment performed was on the action of streptomycin alone, and of streptomycin combined with promizole (Study XII). This experiment was done in immune-allergic rabbits. Inasmuch as the same untreated group served as controls in both the streptomycin alone and the streptomycin plus promizole treated rabbits, these two experiments are shown together. Streptomycin was given in both the treated groups in the dosage of 50 mgms. per kilo of bodyweight per diem, in one dose, and promizole in the dose before outlined, about 1·5 gms. per diem. These dosages gave blood plasma levels up to 7·6 mgms. per cent. for streptomycin, and an average of 1·7 mgms. per cent. for promizole. The period of treatment was two and a half months. The number of rabbits in each group (controls, streptomycin-treated, and streptomycin-plus-promizole-treated) was approximately 20 each.

The results of this experiment are shown graphically in Fig. 13. In both treated groups the results were dramatic. At the end of the second week of treatment, there was a marked difference in favour of the treated groups. At the end of the fourth week this change was striking. The control group had a level of " 2 " for the ocular inflammations, while the treated groups were almost quiescent clinically, the average being 0·25. While the charted averages of activity are practically identical in the two treated groups, the improvement was much more marked in the group

FIG. 14.

Control—February 25—maximum reaction

FIG. 15.

Control—April 28—maximum reaction.

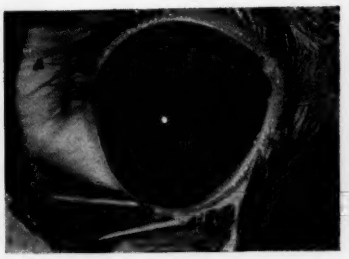


FIG. 16.

Control—February 25—minimum reaction.

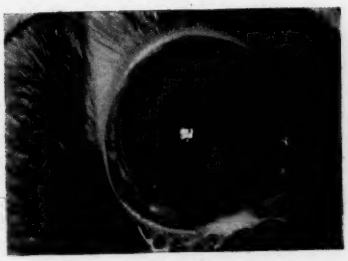


FIG. 17.

Control—April 28—minimum reaction.

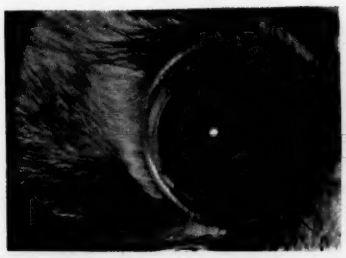


FIG. 22.

Streptomycin-treated—before treatment.

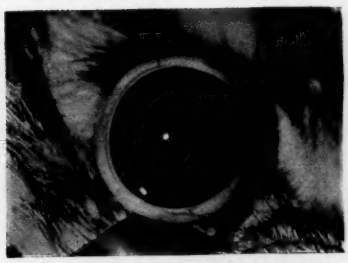


FIG. 23.

Streptomycin-treated—after treatment.

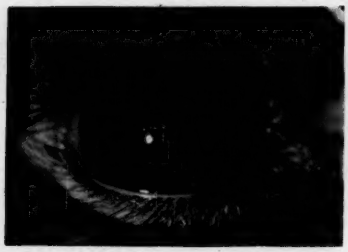


FIG. 24.

Streptomycin-treated—before treatment.

FIG. 25.

Streptomycin-treated—after treatment.

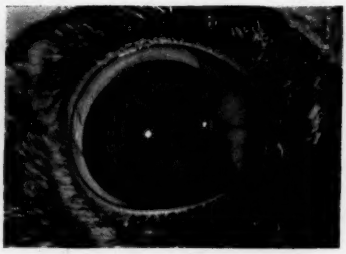


FIG. 30.

Streptomycin-plus-promizole-treated rabbit—before treatment.

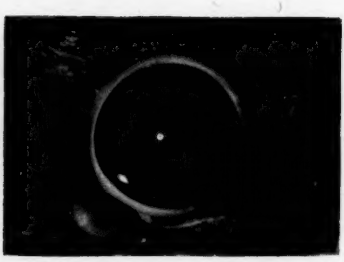


FIG. 31.

Streptomycin plus-promizole-treated rabbit—after treatment.

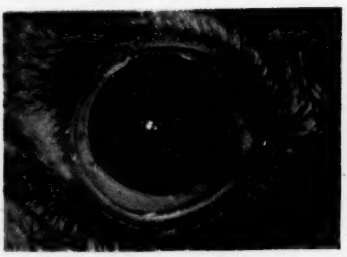


FIG. 32.

Streptomycin-plus-promizole-treated rabbit—before treatment.

FIG. 33.

Streptomycin-plus-promizole-treated rabbit—after treatment.

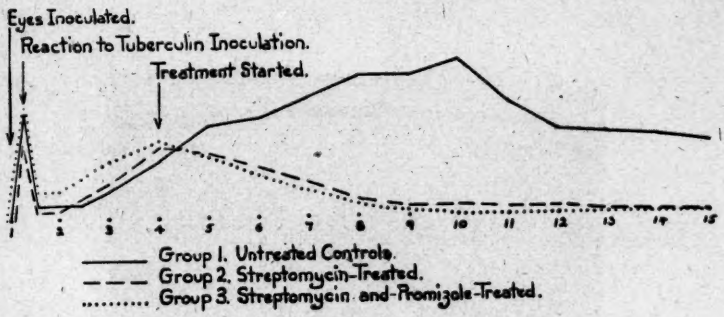


FIG. 13.

The effect of streptomycin alone and streptomycin plus promizole in the immune-allergic rabbit.

treated with the combination of streptomycin and promizole. One apparently non-immune rabbit with a severe and resistant ocular tuberculosis accounted for the greater portion of the activity in the streptomycin-promizole group. The lesions in this rabbit subsided only after twelve weeks of treatment.

The differences in the histological pictures were equally striking. The rabbits of the control group sacrificed for histological study all showed numerous hard tubercles throughout the cornea, iris and ciliary body together with monoculear and epithelioid cell infiltration. The rabbits treated with streptomycin alone showed minimal lesions only. The rabbits treated with a combination of streptomycin and promizole showed no active lesions, the sections showing only scarring, an occasional encapsulated tubercle, and persistence of wandering cells in the iris and ciliary body.

The different clinical course and histological pictures can well be demonstrated pictorially. Thus Figs. 14 and 15, and Figs. 16 and 17, show the high and low extremes in the control group, at the onset of inflammation and at the end of the experiment. Figs. 18-19 show the typical histological picture of untreated tuberculosis in these same control immune-allergic rabbits. Figs. 18-19 illustrate the maximum histological reaction, while Figs. 20-21 illustrate the minimum histological reaction. Figs. 22-23, and Figs. 24 and 25, show the before and after clinical pictures of typical rabbits treated with streptomycin alone, and Figs. 26-29 show the minimal histological lesions in these same rabbits. Figs. 30-31, and Figs. 32-33, show again the before and after clinical pictures of typical rabbits treated with the combination of streptomycin and promizole, and Figs. 34-38, show the total absence of any active histological lesions in these same animals, the evidences of tuberculosis being limited to an encapsulated tubercle and the persistence of wandering cells.

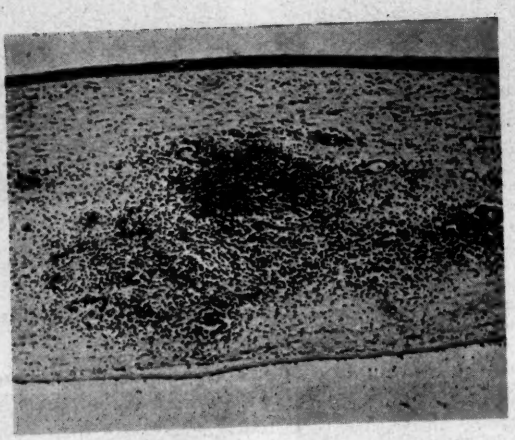


FIG. 18.

Cornea of control rabbit—maximum reaction.

FIG. 19.

Iris of control—maximum reaction.

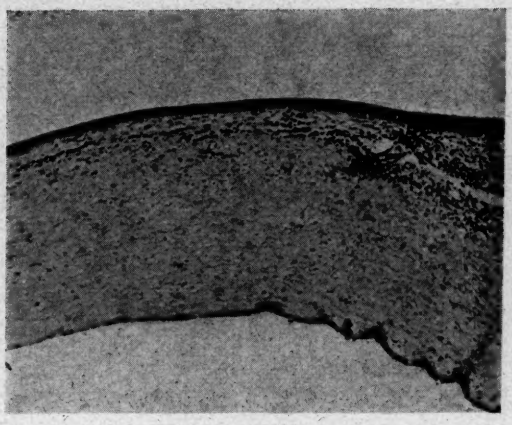


FIG. 20.

Cornea of control—minimum reaction.

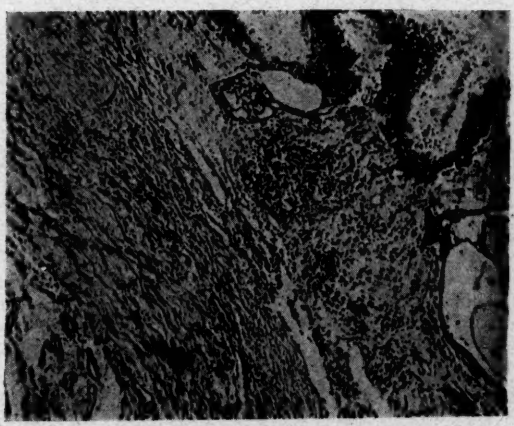


FIG. 21.

Ciliary region of control—minimum reaction.

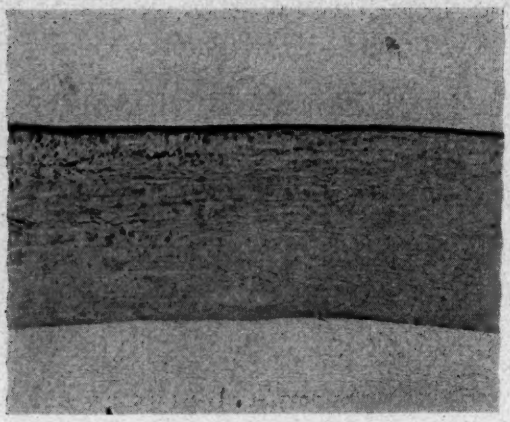


FIG. 26.

Cornea of streptomycin-treated rabbit—minimal infiltration.

FIG. 27.

Iris of streptomycin-treated rabbit—small tubercle on posterior surface. Healed tubercle in stroma.

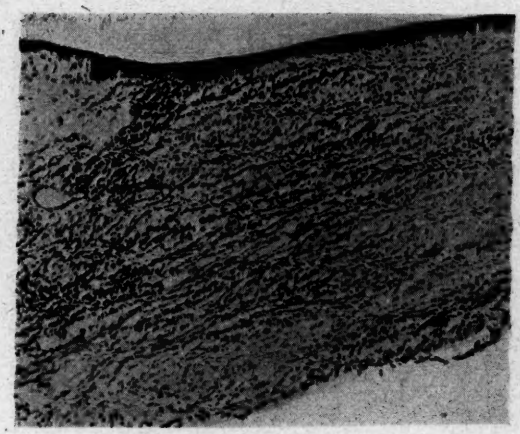


FIG. 28.

Cornea and root of iris of streptomycin-treated rabbit—minimal infiltration.

FIG. 29.

Root of iris and ciliary body of streptomycin-treated rabbit—moderately intense infiltration.

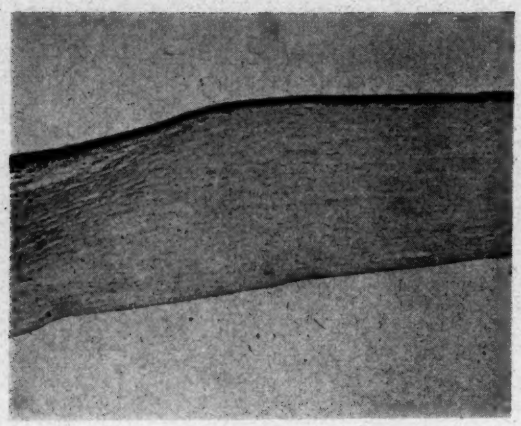


FIG. 34.

Streptomycin-plus-promizole-treated rabbit—minimal scarring.

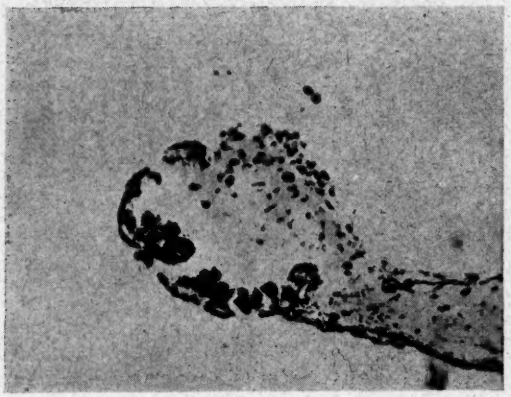


FIG. 35.

Streptomycin-plus-promizole-treated rabbit—healed tubercle at tip of iris.

FIG. 36.

Streptomycin-plus-promizole-treated rabbit — normal anterior ocular segment.

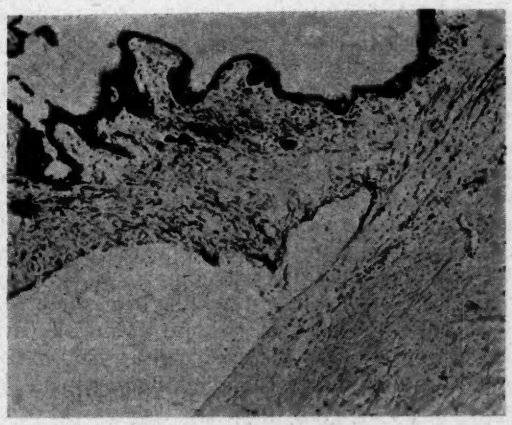


FIG. 37.

Streptomycin-plus-promizole-treated rabbit—minimal scarring of iris, persistence of wandering cells.

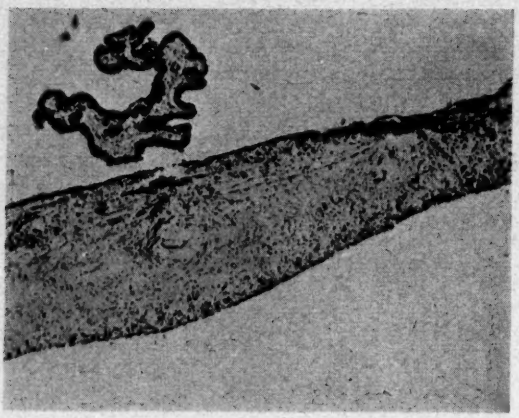


FIG. 38.

Streptomycin-plus-promizole-treated rabbit — showing persistence of wandering cells in iris.

At the conclusion of the therapy, six rabbits in each group were sacrificed for histological study, six others for culture of the dissected-out uveal tracts and for transmission experiments, and the remainder kept under observation for any recurrences of inflammation. The transmission experiment in these rabbits was a much more severe test than that employed in the previous experiment for rabbits treated with promin and promizole alone. The dissected uveas were macerated in only 1·5 c.c. of salt solution, whereas 5·0 c.c. of dilutant had been used in the experiment with promin and promizole alone. The results of these culture transmission experiments, and the incidence of recurrences in the surviving rabbits are shown in Table I. Thus the cultures of all controls were positive, showing from 15 to innumerable colonies in each slant. In the rabbits treated with streptomycin alone, three cultures were positive with 1-3 colonies only, while three were negative. In the rabbits treated with streptomycin and promizole, five cultures were entirely negative, while the sixth culture showed no macroscopic colonies, but bacilli were found on microscopic examination.

On transmission experiments, all the uveal tracts of the control group were infectious. In both the streptomycin-treated rabbits and the streptomycin-promizole-treated rabbits, 50 per cent. of the uveal tracts were infectious, and 50 per cent. non-infectious.

Recurrences occurred in three out of nine surviving rabbits treated with streptomycin alone, the average remission period

	Transfer		Cultures of Uveal Extracts		Recurrences	
	Results	Incubation Period	Results	Incubation Period	Results	Remission Period
Group I (untreated controls)	100% positive.	17 days	100% positive.	Heavy growth in 4 weeks.	gradually waning activity.	
Group II (Streptomycin alone)	50% (3) positive. 50% (3) non-infectious.	26 days	50% (3) positive for tubercle bacilli 50% (3) neg.	1-2 colonies in 5 weeks.	3 out of eight (37%)	12 days (average)
Group III (Streptomycin + Promizole)	50% (3) positive. 50% (3) non-infectious.	33 days	83% (5) negative. 17% (1) positive.	microscopic growth in one culture only in 8 weeks.	1 out of nine (11%) (minimum reaction)	34 days

TABLE I.

Results of transfer experiments and cultures and incidence of recurrences.

being 12 days. In the streptomycin-promizole treated rabbits, there was one recurrence in nine rabbits, the remission period being 34 days. Resistance experiments on the recovered organisms are as yet incomplete.

From these studies on the action of sulphones and antibiotics in ocular tuberculosis, it is conservative to conclude that a relatively non-toxic sulphone, promizole, has a deterrent action on the local tuberculous lesion in the immune-allergic rabbit. The deterrent action is far from absolute, and at best is scarcely more than sufficient to restrain the growth of the bacilli, or attenuate their virulence, to within the bacteriostatic or bactericidal range of a fairly well-developed immunity. Streptomycin has a much more powerful therapeutic action, undoubtedly a true bacteriocidal action, but again, as administered in these experiments, this action is not always absolute. The combined action of streptomycin and promizole is much more pronounced, and appears to eradicate the bacilli from the infected tissues in a large percentage of the treated cases, and certainly to curtail their growth and virulence in the remaining cases.

SUMMARY

These experimental findings may be summarized as follows: It appears that Rich's law for the pathogenesis of tuberculous lesions holds true in localized ocular tuberculosis. The factors governing the course and character of the lesion are the number and virulence of the infecting organisms, the degree of tissue hypersensitivity present, and the amount of the resistance established by the host. These studies also offer an explanation for the

relative cutaneous anergy often present in animals and man with inflammatory tuberculous lesions of the eye.

This concept of the pathogenesis of a tuberculous lesion offers obvious points for therapeutic attack on the disease. The first of these is enhancement of immunity, and nothing specific has been done as yet to stimulate local resistance artificially. The second is removal of the fatal tissue hypersensitivity, and this can usually be accomplished by the use of tuberculin as a desensitizing agent, and has a distinctly beneficial effect on the clinical course of the lesion. The third is the direct attack on the tubercle bacilli, and in streptomycin and promizole combined, we have a powerful weapon to this end. Doubtless other better antibiotics and sulphones will be found, but at present this combination appears the best available.

THE VASCULAR ACTION OF PILOCARPINE, ESERINE ADRENALINE AND ATROPINE, AND THEIR INFLUENCE IN PRIMARY CHRONIC GLAUCOMA*

BY

G. CRISTINI

BOLOGNA

THE rationale of the action of miotic and mydriatic drugs in glaucoma is a matter which still retains its importance, not only because our knowledge of the mechanism of the action of these drugs is still incomplete, but also because the discovery of new antiglaucomatous drugs and modern researches on the chemical mediation of the transmission of nerve impulses have amplified the problem without offering any substantial explanation. Moreover, the interpretation of the mechanism of these drugs—still an unsolved problem when they act upon the normal eye—becomes more complicated when they are considered in relation to the added problems involved in the development of a raised intraocular pressure in glaucoma.

In physiological literature we find the most diverse views regarding their effect on the ocular tension and the vascular system in the eye. Without mentioning Leber's notes in "Graefe Sämisch Handbuch," but reviewing the opinions of recent authors only, we find that in Colombo's opinion eserine and pilocarpine cause vasoconstriction, whereas Bailliart and Bidault attribute to

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these same drugs a vasodilatory influence, particularly marked and visible in the conjunctival vessels; Michail and Vancea are in agreement with them. In Wessely's opinion eserine causes vasoconstriction in the conjunctival vessels and vasodilatation in the vessels of the iris and the ciliary body. Dieter and Thiel, on the ground of experimental findings, also suggest that these drugs cause a vasodilatation. Koellner, in a case of persistent pupillary membrane in man, was likewise able to observe a vasodilatation. Atropine, according to Colombo, causes vasodilatation as also does cocaine, a view with which Michail agrees; while according to Bailliart and Dieter, the action of this drug is vasoconstrictive. Among the most exhaustive physiological researches on this subject are those of Colle, P. M. Duke-Elder and W. S. Duke-Elder. On the basis of direct observation of the vessels of the iris, the registration of contractions of the extra-ocular muscles, temperature records taken in the anterior chamber and the measurement of the intra-ocular pressure in healthy animals and in artificially perfused eyes, these authors reached the following conclusions with regard to the relations of muscle contraction, vasomotor action, size of the pupil and their influence on the ocular tension:

"Adrenaline in small doses dilates the capillaries, increasing their permeability and raising the intra-ocular pressure; in large doses it constricts the vessels, lowering the intra-ocular pressure; in any dose it stimulates the plain muscle of the orbit, raising the intra-ocular pressure, and dilates the pupil, which is without effect on the intra-ocular pressure.

"Atropine dilates the minute vessels and increases their permeability, thus raising the intra-ocular pressure, and relaxes the plain muscle of the orbit, thus lowering the intra-ocular pressure.

"Physostigmine dilates the small vessels and increases their permeability, and also increases the tone of the voluntary muscles of the orbit, thus increasing the intra-ocular pressure.

"'Pituitrin' constricts the arterioles, lowering the intra-ocular pressure, and stimulates the plain muscle of the orbit, raising the intra-ocular pressure.

"Histamine dilates the minute vessels and increases their permeability, raising the intra-ocular pressure, provided these have sufficient tone; otherwise its action is confined to a constriction of the arterioles, an action which lowers the intra-ocular pressure.

"Choline dilates the minute vessels and stimulates the voluntary striped muscles of the orbit, raising the intra-ocular pressure. Nicotine manifests its action entirely by stimulating the plain and striped muscle of the orbit to contract, thus raising the intra-ocular pressure.

"Curare lowers the intra-ocular pressure by relaxing the tone of the voluntary muscles."

On interpreting the action of these miotic and mydriatic drugs in glaucoma, however, all the hypotheses which have been advanced do not seem to fit in accurately with the results obtained with these physiological researches. Among the more popular hypotheses, Weber's is the most frequently quoted: the decrease in ocular tension determined by the use of miotic drugs in primary

glaucoma is due to a better outflow of the aqueous humour through Schlemm's canal resulting from the pulling away of the root of the iris from the posterior surface of the cornea. The prompt and, in some instances, considerable diminution of tension in cases of glaucoma with gross anatomical changes at the filtration angle, as in cases of synechiae of the root of the iris with the posterior surface of the cornea, or in cases where the canal of Schlemm is absent, as in hydrophthalmia, puts a limit to the validity of this hypothesis. Similarly, Hamburger's hypothesis, according to which miotic drugs favour the opening of the lymphatic pathways of the iris through an increase of the absorbing surface of this membrane, does not explain the diminution of ocular tension, particularly in those cases wherein the uveal tissue shows large areas of atrophy. The demonstration that the aqueous humour is very similar to a dialysate made the influence of the size of the pupillary diameter on ocular tension a matter of little importance (Duke-Elder). A further hypothesis among those commonly recorded is that of Kuesel and Fortin, by which it is suggested that the hypotensive effect of miotics is due to the contraction of the ciliary muscle by which not only are Fontana's spaces opened up owing to the pull on the scleral spur, but also the arterial inflow is reduced in consequence of a compression of the long posterior ciliary arteries as they traverse the muscular network of the ciliary body.

It seems peculiar that so little importance has been attributed to the purely vascular effect exerted by the miotic drugs: this action has been proved experimentally to be characteristic, and nowadays there can be little doubt that changes in the uveal circulation constitute one of the main causes of the development and rise of intra-ocular pressure in glaucoma. This, by the way, was the explanation offered regarding the effect of adrenaline in glaucoma, and it is now clear that this drug acts merely by a modification of the circulatory rate. Dieter is among the few who believe, without, however, giving a very clear explanation, that the effect of pilocarpine and eserine depends only on a simple vascular action. It is to be noted also that Thiel, who found experimentally a dilatatory influence of pilocarpine and eserine on the uveal vessels, is of the opinion that these drugs remove vascular stasis in glaucoma through a widening of the uveal vessels and an increased arterial "debit." He believes, however, that this action is not responsible for the entire effect and that further factors, such as a greater unfolding of the iris, are involved.

The problem of the action of miotics and mydriatics in glaucoma is substantially connected with the development and rise of intra-ocular pressure in this disease. In previous experimental

researches I have already formulated some considerations about the pathogenesis of this symptom, suggesting that one of the main causes is an alteration in the uveal circulatory " debit." For this reason, in the present paper attention is drawn to the vascular action of the most common miotic and mydriatic drugs, analysing in particular their effect in glaucoma.

EXPERIMENTAL FINDINGS

The eyes of albinotic rabbits were studied and, in order to obtain experimental demonstrations of the vascular effects of adrenaline, pilocarpine, eserine and atropine on the iris, the ciliary body and choroid, the following techniques were adopted.

I

Watery solutions of 1 per cent. atropine, 2 per cent. pilocarpine, 0·5 per cent. eserine were instilled several times into the conjunctival sac of the experimental animals, and some drops of adrenaline in 1 : 1000 solution were injected under the conjunctiva. Subsequently, after half an hour, one, and two hours, when an intense miotic or mydriatic effect had appeared, the eyes were examined with the slit-lamp, the light from which was filtered through a chamber filled with copper sulphate solution and a Uviol filter. The vessels of the iris, which were of a black bluish colour in the filtered light, were examined through a corneal microscope (ocular 2, objectives 4 and 6 Zeiss).

From biomicroscopical examination, the following observations were made :

Adrenaline (Fig. I).

Both the circulus iridis major and the anterior arterioles branching radially from this circle were very thick and winding in comparison with the control eye. Near the pupillary border and, less dense, in the ciliary portion of the iris, one could, with strong magnification, make out the presence of a fine network of capillaries running parallel to the pupillary border. Contrary to Leber's findings, I could observe that this network, especially near the pupillary border, permits the formation of anastomoses between the terminal branches of the anterior arteries of the iris. Just above the pupillary border some small capillary arches were found that could likewise be observed in the control eye, although limited in number.

Pilocarpine and eserine (Figs. 5 and 8)

Observations with these two drugs are considered together because the biomicroscopic findings were analogous. In contrast to the control eye, it was found that the circulus iridis major and the anterior radial iridal arterioles as well as the two trunks of

FIG. 1.

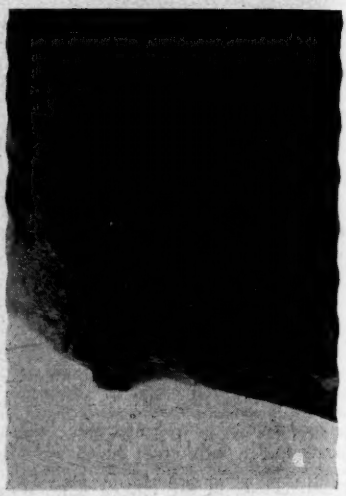

FIG. 2.

FIG. 3.

FIG. 4.

Adrenaline: Partly schematic drawing of the vessels of the iris as seen with the slit-lamp (Fig. 1), and microphotographs of the iris after the benzidine reaction (Figs. 2–4). The dilatation of both the large vessels and the capillaries accompanied by the appearance of new vascular districts, especially in the pars pupillaris is characteristic.

FIG. 5.

FIG. 6.

FIG. 7.

Pilocarpine: Partly schematic drawing of the vessels of the iris as seen with the slit-lamp (Fig. 5). and microphotographs of the iris after the benzidine reaction. Presence of numerous fine capillaries over the whole surface of the iris (Fig. 6), while the larger radial vessels appear normal in size and even reduced (Fig. 7).

the long posterior ciliary arteries which form the circulus iridis major in the rabbit did not appear dilated, whereas near the pupillary border these vessels divided in numerous small capillary arches. Moreover, towards the ciliary portion among the anterior radial arteries numerous small vessels were observed, forming a sort of capillary network.

Atropine (Fig. 11)

Here one is struck by an abnormal dilatation of the circulus iridis major and of the anterior arteries of the iris. I could not see any capillary network as in the preceding experiments. Near the pupillary region, however, I found some loop-formed arches, as are seen in normal eyes.

II

The eyes were subsequently enucleated from the surviving animals. The globes were cut parallel to the equator a few mm. behind the limbus. The lens and vitreous body were carefully removed. The iris as well as the retina and the choroid were detached from their bases in small rectangular fragments and examined with the dissection microscope. The microscopical findings were mostly analogous to those obtained biomicroscopically, so far as the anterior surface of the iris was concerned.

Adrenaline (Figs. 2-4)

The ciliary processes, in comparison with the control eye, appeared congested not only because of the dilatation of the arterioles but also because of an increase in their number. Near the pupillary border and throughout the whole surface of the iris I found tiny capillaries which did not occur in the control eye.

Pilocarpine and eserine (Figs. 6, 7, 9, 10).

The striking feature of the microscopical picture was the presence of numerous very fine capillaries uniting the single arteries, and the presence near the pupillary border of numerous capillary arches resembling a kind of ***caput Medusae.*** Inside the ciliary processes I found fewer vascular trunks than with adrenaline, at the most two or three, as occur in the normal eye. I cannot assert with certainty to have found any differences from the normal in the fragments of choroid examined. On the whole, the vascular dilatation here was less intense than after adrenaline and atropine.

Atropine (Figs. 12-13)

Microscopically the thin capillary network seen in the pupillary portion of the iris after the administration of pilocarpine and eserine was not seen, but there were scattered and irregular loop-formed capillary arches. In the choroid I observed a vascular dilatation which had been absent in the preceding cases.

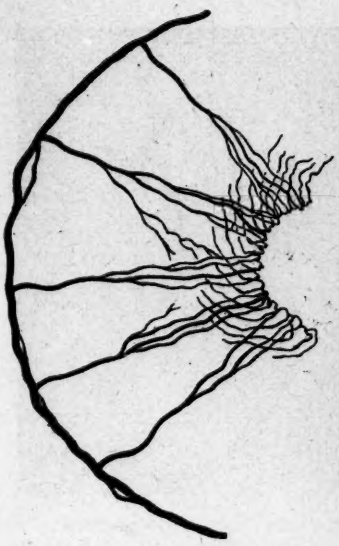

FIG. 8.

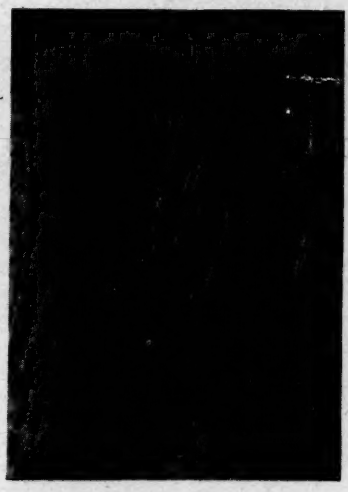

FIG. 9.

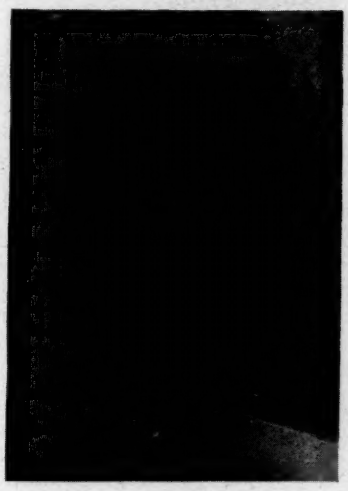

FIG. 10.

Eserine: Partly schematic drawing of the vessels of the iris as seen with the slit-lamp (Fig. 8), and microphotographs of the iris after the benzidine reaction (Figs. 9 and 10). Appearance of numerous new capillary districts with dilatation of the smaller vessels, especially in relation to the pars pupillaris, without a corresponding dilatation of the large radial vessels of the iris.

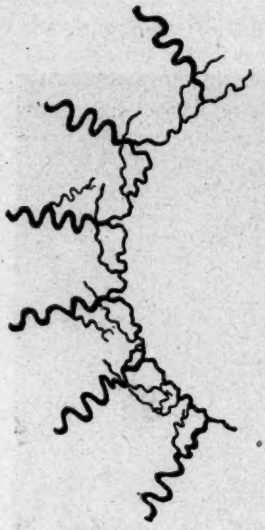

FIG. 11.

FIG. 12.

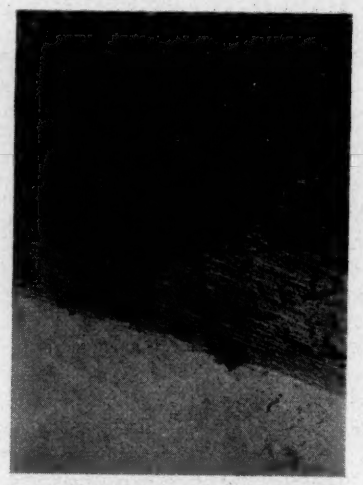

FIG. 13.

Atropine: Partly schematic drawing of the vessels of the iris as seen with the slit-lamp (Fig. 11), and microphotographs of the iris after the benzidine reaction (Figs. 12 and 13). Considerable vasodilatation and tortuosity of the large vessels of the iris without corresponding dilatation of the smaller vessels, and appearance of new capillary districts. The pars pupillaris does not show any tiny vessels (Fig. 13).

III

The fragments were subsequently fixed in a concentrated solution of common salt, sugar and formalin for three days, and finally the benzidine reaction (Pickworth's method) was performed.

From these biomicroscopic and microscopic findings, both in a fresh state and after the benzidine reaction, the following conclusions emerge which, incidentally, are in agreement with those of most investigators:

Adrenaline.—Arterial vasodilatation (probably also venous dilatation) and capillary vasodilatation followed by the appearance of new vascular districts.

Pilocarpine and eserine.—Capillary vasodilatation and opening of new capillary districts, without dilatation of the larger vessels.

Atropine.—Marked arterial vasodilatation (and probably also venous dilatation) without corresponding capillary vasodilatation and without appearance of new capillary districts.

DISCUSSION

The vasodilator effect obtained by the four drugs is clearly demonstrated by the preceding observations; but while atropine merely acts upon the larger vessels, adrenaline acts upon the capillaries as well, producing not only vasodilatation but also the appearance of new vascular districts. Pilocarpine and eserine exert their action on the capillary vessels with the opening of new vascular sections.

The difficulty in elucidating the effect of these drugs in primary glaucoma, especially with regard to their vascular action, derives from the fact that in this disease the conception of von Hippel and Gruenhagen is usually considered axiomatic. According to it a uveal vasodilatation is constantly followed by a rise in the intra-ocular pressure. As long ago as 1905 Angelucci questioned this physiological conception, which was based merely upon the experimental findings resulting from stimulation of the trigeminal nerve. Modern knowledge of general and ocular physiology has, however, raised doubts as to the validity of this conception.

Although the dialysis theory, *i.e.*, that the aqueous humour is a dialysate in thermodynamic equilibrium with the blood, does not now appear to explain all the facts (Duke-Elder and Davson), it is, however, indisputable that the height of the intra-ocular pressure must be regulated to a large extent by the hydrostatic pressure of the uveal capillaries and by colloid osmotic pressures. According to this conception, which has been generally accepted up to recent times, the intra-ocular pressure is established by the mean level of the capillary pressure less the colloid-osmotic pressure of the plasma proteins (Parsons; Henderson and Starling; Dieter; Duke-Elder; Magitot). The corollary to this

relationship is that a rise in the level of capillary pressure determines a rise in intra-ocular pressure when the colloid osmotic pressure of the plasma proteins remains unaltered.

General haemodynamic laws inform us that the hydrostatic pressure at any level of the vascular system is " proportional to the sum of resistances the liquid is forced to overcome " (Luciani). The conception of von Hippel and Gruenhagen, which we have already noted, may hold true, according to haemodynamic laws, only in the case of dilatation of the arteries, but not of the capillaries. Here, indeed, haemodynamics show that the sum of resistances increases instead of diminishing, as in the case of arterial dilatation, in spite of a considerable increase of the vascular bed. The corollary to this fundamental physiological fact is that two different variations in intra-ocular pressure occur according to whether there is an arterial or a capillary vasodilatation. In the former case, the sum of resistances encountered by the blood decreases, and therefore the mean capillary pressure increases, and this is followed by a rise in intra-ocular pressure; in the latter case, in spite of the considerable dilatation of the vascular bed, the sum of resistances increases and is followed by a fall in hydrostatic capillary pressure, and consequently in intra-ocular pressure.

The importance of these facts must be clearly remembered in any discussion on the regulation of the tension of the eye. The functional independence of the arterial circulation from the capillary circulation is certainly one of the most essential features in maintaining the intra-ocular pressure at a constant level, in spite of occasional sudden haemodynamic variations. In pathological conditions, as in primary chronic glaucoma, we must not forget that the rise of capillary pressure is one of the fundamental experimental findings (Dieter). Notwithstanding numerous experimental researches, no variation in blood composition or in the colloid osmotic pressure of the plasma proteins has been found in this disease.

The rise of the capillary pressure level in glaucoma, in haemodynamic terms, may be considered as a " *diminution of the sum of peripheral resistances encountered by the blood as far as the last capillary barrier.*"

From my previous experimental researches I concluded that one of the numerous causes of the rise in intra-ocular pressure in the glaucomatous eye is such a diminution of the sum of resistances. According to this hypothesis the cause is a reduction of the uveal capillary bed owing to the obliteration of numerous vascular districts. This hypothesis was based on the fact that in typical primary (simple) chronic glaucoma the choroid becomes thinner

and the capillaries are obliterated and disappear, as was particularly stressed by Elschnig. Further evidence is the fact that no rise in capillary pulse volume could be registered photoplethysmographically on the inspiration of amyl nitrite.

The effect of the action of pilocarpine and eserine, adrenaline and atropine, so characteristic in this disease, can be related with this essential aspect of the development and rise of intra-ocular pressure.

Pilocarpine (2 per cent.) and eserine (0·5 per cent.).

From a vascular point of view these drugs act by modifying the capillary circulatory "debit." As was already mentioned in the experimental part of this paper, their vasodilator action makes itself evident on the capillary vessels, even favouring the opening up of new vascular reserve sections. This was suggested by Krogh in 1924 at the Deutsche Ophthalmologische Gesellschaft, in view of the fact that the instillation of these drugs raises the albumen content of the aqueous humour, and has also been experimentally confirmed by Angelucci, Wessely, Dieter, and others. As has already been mentioned, the dilatation of the capillary bed will give rise to an increase in the sum of resistances and this increase cannot be compensated by a growth of the vascular bed. Consequently we shall note a fall in the level of the capillary pressure.

Indeed, by measuring the capillary pressure entoptically in glaucomatous patients Dieter found that this pressure falls after the instillation of miotic drugs. Again, Thomassen has recently observed in glaucomatous patients that the instillation of pilocarpine and eserine lowers the venous pressure in the episcleral vessels, whereas it is without any influence on the pressure in the episcleral arteries. Moreover, this author found experimentally that the lowering of intra-ocular pressure was secondary to the decrease in venous pressure.

Finally, the present hypothesis that pilocarpine and eserine increase the sum of resistances by dilating and opening new capillary districts may explain some experimental findings that have not yet found a solution. Gala, by means of sodium iodide, and Thiel, by means of fluorescein, found that in glaucomatous eyes after the instillation of miotic drugs the outflow of these substances into the aqueous is lessened, thus confirming Hess's entoptic findings as to the slowing of the blood flow.

In fact, following general physiological principles, the increase of the capillary bed brought about by pilocarpine and eserine will lower the capillary pressure as well as the rate of flow.

Atropine (1 *per cent.*).

My findings show that this drug produces vasodilatation in the larger vessels and has no influence whatever on the capillary bed. That its action on the capillaries is almost without effect is demonstrated by the fact that the instillation of this drug does not alter the concentration of albumen in the aqueous, as was found by Dieter and confirmed quite recently by Stocker. According to general haemodynamic laws, the arterial vasodilatation induced by this drug will determine a diminution of the sum of resistances in the glaucomatous eye. Dieter, indeed, found experimentally that the capillary pressure rises with the instillation of atropine. Since this occurs in a third of all glaucomatous patients, and when it does there develops at the same time an acute attack of raised tension, we may infer that in these cases the capillary bed, owing to its severe impairment, is no longer able to neutralize the diminution of the sum of resistances which follows the vasodilatation of the large arterial vessels. The consequence will be a rise in intra-ocular pressure and an infringement of the " law of circulatory rate," *i.e.*, the amount of blood passing through the the arterial section is not exactly equal to the amount passing during the same time through the venous section of the system. This would be comparable to the onset of certain pulmonary oedemas occurring in consequence of the altered ratio between the amount of blood passing through the pulmonary veins and the amount passing during the same time through the arterial pulmonary system.

Adrenaline (1 : 1000).

The vascular effects of adrenaline are to some extent similar to those already inferred for pilocarpine and eserine as well as for atropine. It is beyond doubt—and most investigators are of this opinion—that the greatest hypotensive effect obtained with this drug becomes evident during the period of maximal arterial and capillary vasodilatation. Like atropine, this drug actually dilates the large arterial vessels, thus diminishing the sum of resistances; but like pilocarpine and eserine it opens new vascular reserve sections, thus increasing the capillary surface. But the final result is an increase of the sum of resistances, owing to the growth of the capillary bed, thus bringing about a decrease of the mean capillary hydrostatic pressure.

This drug is probably contra-indicated in acute glaucoma because under certain experimental conditions, as was noticed by Poos, it produces an excessive permeability in the capillaries for the plasma proteins, and thus will determine a marked rise in intra-ocular pressure. In fact, as the balance of distribution is

almost equal inside and outside the vessels, an annulment of the osmotic membranes takes place, as if a river of fresh water enters into the sea. The level of the intra-ocular pressure would thus be determined only by the height of the vascular hydrostatic pressure, no longer antagonized by the colloid osmotic pressure of the plasma proteins, as in the equilibrium described by Henderson and Starling.

Finally, I wish to emphasize that the hypotheses so far put forward represent only an attempt to interpret the vascular action of these four drugs, and that further experimental investigation is required. As long as our knowledge of the origin and nature of the intra-ocular fluid is imperfect, however, it is impossible to offer a definite and complete explanation regarding the effects of these drugs, since the questions raised are intimately connected with the more essential problem of the development and rise of the intra-ocular pressure.

SUMMARY

1. Pilocarpine and eserine determine a vasodilatation and the opening of new capillary districts followed by an increase of the capillary bed without, however, dilating the large vessels. In the light of general haemodynamic knowledge this causes an increase of the sum of resistances in the circulation, in spite of a considerable growth of the circulatory bed. The fundamental corollary to this action is the fall of the mean capillary hydrostatic pressure and, therefore, of the ocular tension, as occurs in primary chronic glaucoma.

2. Atropine determines a dilatation of the large vessels without any corresponding capillary dilatation, and without opening up new vascular districts. According to haemodynamic laws, this brings about a diminution of the sum of resistances in the circulation, and therefore an increase of the mean capillary hydrostatic pressure, whenever the capillary bed, as in chronic glaucoma, is severely impaired and is no longer able to cope with such difficulties.

3. Adrenaline determines a dilatation both of the large vessels and of the smaller capillaries, followed by the opening of new vascular districts and by a growth of the circulatory bed. Like atropine, this drug dilates the large arterial vessels, thus diminishing the sum of resistances; but, like pilocarpine and eserine, it opens new vascular reserve sections, thus increasing the capillary surface. But the final resulting effect is the increase of the sum of resistances owing to the growth of the capillary bed, thus bringing about a decrease of the mean capillary hydrostatic pressure, and therefore of ocular tension.

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SLIT-LAMP EXAMINATION OF THE VITREOUS AND THE FUNDUS*

BY

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EXAMINATION of the vitreous body and of the fundus with the help of the slit-lamp enables us to understand better some pathological pictures, and often facilitates a differential diagnosis. Since more details are being revealed by this method, pathological changes can be detected early. Moreover, stereoscopic examination of the fundus is made possible by a cheap additional device to the slit-lamp which not only does the work of a binocular ophthalmoscope of Gullstrand, but gives better results.

* Lecture given May 8, 1948, to members of the British Faculty of Ophthalmologists at Berne.

The method consists in reducing as much as possible the angle between the illuminating arm and the microscope of the slit-lamp by means of a special prism (Fig. 1), and in eliminating the refraction of the cornea. We obtain this result with the help of a contact glass made of plastic. Instead of a contact glass, Lemoine and Valois, and later Hruby, used a concave lens of 55 dioptres in front of the eye. The contact glass affords a great field of vision, and in general cleaner pictures of the fundus when observed with a 20x magnification; it can be centred on the eyeball very easily. The astigmatic distortion in 20x magnification can be made very

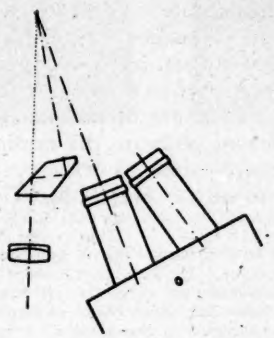

FIG. 1.

small, and even reduced to zero—especially if one examines with a short slit—when the point examined lies in a region about 25° round the posterior pole. By 10x magnification, this region is still greater. In certain cases—for instance shortly after intra-ocular operations—the concave lens is preferable.

In such an examination, the most important point is to see the vitreous and the fundus *stereoscopically*. This is the chief condition for seeing fine details and avoiding deceptive pictures. After having dilated the pupil to a maximum, one always succeeds in seeing a great part of the fundus stereoscopically. The apparent place of the object observed with our model of the slit-lamp (Haag-Streit) being in the axis of revolution of the whole instrument, the picture does not move if the microscope and illuminating arm are turned about this axis. Thus one always finds a position where the observed point of the fundus is seen stereoscopically. Lateral movements of the instrument make other points of the fundus appear in the field of the microscope.

For examination of the vitreous the angle between the illuminating arm and the microscope is made as wide as possible if one

wishes to eliminate the reflected light from the fundus during the examination in focal light.

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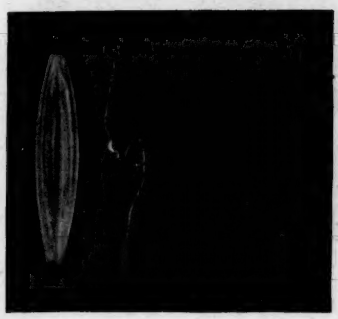

FIG. 2

Hans R. aged 28 years. R. eye. State after juvenile haemmorrhage into the vitreous detachment of the vitreous. Illumination from the left side. 10×.

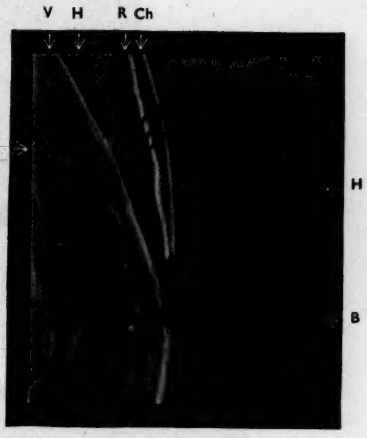

FIG. 3

Fritz S. aged 55 years. R. eye. M: site of the macula. P: site of the papilla. V: back border of the detached vitreous. R: detached retina. Ch: Choroid. H: triangular hole in the retina. B: pre-retinal haemorrhage in the pocket between detached vitreous and retina. Illumination from left. 20×.

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Fritz A. aged 55 years. R. eye. Retinitis proliferans diabetica. Vascularisation of the back vitreous membrane. V: Section of the back membrane of the vitreous. R: Section of the retina. The vessels of the membrane are visible directly on its section and in the light reflected by the fundus. 20×.

FIG. 5

Jakob B. aged 35 years. R. eye. Chorioretinitis centralis serosa. Illumination from the left side. 20×.

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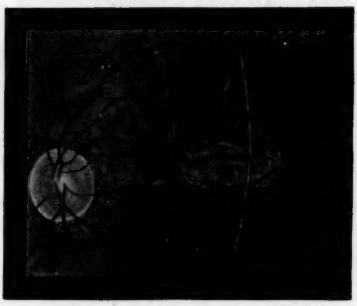

FIG. 12

Erika M. aged 68 years. L. eye. Old focus of choroiditis centralis with depressed choroid and thinned retina.

the posterior vitreous space. In cases of periphlebitis retinae, the posterior limiting membrane of the vitreous is detached from the retina and the vessels of the proliferating scars are situated in this membrane (Bangerter-Blaser, Hruby) (Fig. 4). At the onset of many retinal diseases (for instance chorioretinitis), the posterior limiting membrane of the vitreous is detached from the retina and visible in the optical section as a very fine greyish line. In the reflected light of the fundus, in such cases, one often sees in it fine precipitates.

Slit-lamp examination of the fundus is the best method for examining the posterior part of the retina, especially the macula. If one examines the retina in the large pencil of the slit-lamp the slightest traces of irregularities in thickness appear as irregularities of the surface reflexes.

By observing a normal retina with the slit-lamp, one sees very clearly the configuration of the papilla, the nerve fibres of the retina, the depression of the fovea, and the thickness of the retina in the cross-section. The thickest part of the normal retina is situated on the temporal side of the papilla and around the macula, where one sees, by ophthalmoscopic examination, the wall-reflex of the macula. The normal retina is thinnest at the fovea.

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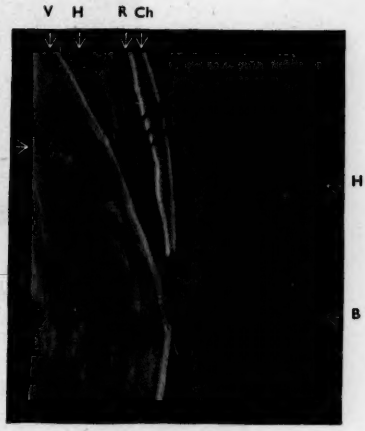

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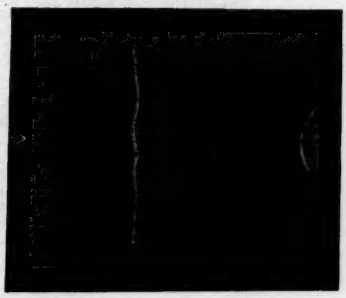

FIG. 5

Jakob B. aged 35 years. R. eye. Chorioretinitis centralis serosa. Illumination from the left side. 20×.

FIG. 6

Werner R. aged 40 years. L. eye. Retinitis centralis serosa para fovealis with detachment of the vitreous.

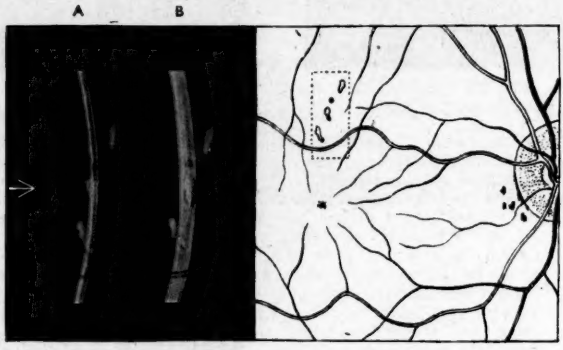

FIG. 7

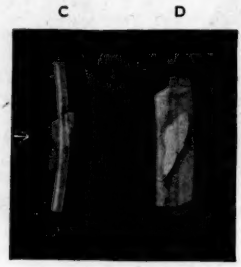

FIG. 7 (a)

Louis L. aged 60 years. L. eye. Retinitis diabetica. Capillarosis spots. –Situation *vide* sketch. (A) narrow slit 20×. (B) wider slit 20×. One sees the shadow of the one spot on the choroid. (C) and (D) the same as (A) and (B) schematized at 40× magnification to show more clearly the site of the capillarosis spots in the thickness of the retina (C) and the shadow on the choroid.

FIG. 8

Ida G. aged 58 years. R. eye. Drusen of the choroid. 20×.

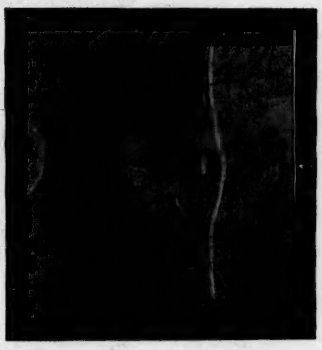

FIG. 9

Alfred G. aged 29 years. L. eye. Ablatio retinae post-traumatica peripherica. Cystic oedema of the macula. Illumination from the right side. 20×.

FIG. 10

Anna St. aged 76 years. L. eye. Hole in the macula. Typical thickened and opaque borders.

FIG. 11

Rosa I. aged 35 years. L. eye. Choroiditis disseminata. In the upper part fresh inflammation; beside the papilla old foci.

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Later on, it becomes slightly marbled. This disease is often mistaken for retrobulbar neuritis, for it is accompanied by a relative central scotoma, generally with only little decrease of visual acuity. Subjectively, there is a yellowish positive scotoma, best visible just after awaking; metamorphopsia exists, easily demonstrable by means of the Amsler lattice. During the disease, the refraction is more hypermetropic than before or after. All these characteristic signs are less pronounced if the changes are situated away from the fovea (Fig. 6). Then the complaints of the patient are indistinct: slightly blurred vision, and a certain distortion of lines. In such cases, the correct diagnosis is seldom made without an examination with the slit-lamp. One mostly assumes nervous disorder, especially because chorioretinitis centralis serosa is often found in vasolabile individuals. The aetiology of this affection is not known, but vasolability seems to favour it. As therapy, we use with success a series of intravenous injections of mercury cyanide (daily 1 c.cm. 1 per cent. solution, 20x) with the usual control of urine and mouth. This disease is not rare, but often overlooked.

3. With the help of biomicroscopy of the fundus, it is very easy to discern little spots of capillarosis from Drusen of the choroid. Capillarosis spots (as signs of a vascular disturbance of the retina) are situated within the thickness of the retina and are always opaque and white; with the slit-lamp often one sees their shadows on the screen of the choroid (Fig. 7). Drusen are situated on the surface of the choroid; their colour is generally yellowish (Fig. 8). When illuminating their neighbourhood, one often sees a golden reflex on their borders. But there exist also little white inclusions on the surface of the choroid not protruding from it. The ophthalmoscopic picture they present is like that of capillarosis spots. Only by the slit-lamp is differentiation possible.

4. Oedema of the retina can be seen very easily. Cystic oedema of the macular region has an extremely beautiful aspect (Fig. 9). The differential diagnosis between cysts of the macula and holes in the macula—which is very difficult with other methods—is very simple by means of biomicroscopy.

A cyst of the macula has an anterior wall which does not appear in the case of a hole (Fig. 10). Little cysts are often more easily visible by indirect illumination than in the focal light of the slit-pencil. Cystoid oedema of the macula is frequent in cases of uveitis, vascular disturbances of the posterior pole of the retina and the choroid (for instance thrombosis of the central vein, arteriosclerotic changes of the choroidal vessels at the macula); in degeneratio disciformis maculae (Junius-Kuhnt); in older detachments of the retina, also sometimes in re-attached cases. However, there are rare cases of cystoid oedema without an assignable cause.

In cases of malignant hypertension, one frequently finds considerable oedema of the retina (without cysts), together with capillarosis spots, haemorrhages and " cotton-wool " degenerations of the nerve fibres. This oedema is very turbid, so that the choroid is seen only indistinctly. On the other hand, in many cases of pure diabetic retinopathy and in Junius-Kuhnt disciform degeneration, a glass-like thickening of the retina appears, so transparent that the shadows of the retinal vessels are seen clearly on the surface of the choroid. The layer where a haemorrhage is situated can be determined exactly.

5. The normal surface of the choroid is smooth. With some aged people it looks rough, as if treated with emery paper. In certain cases it gives the impression that this picture preceded a Junius-Kuhnt disciform degeneration.

6. The differential diagnosis between a detachment of the retina and a tumour of the choroid may be difficult. But if one sees, with the slit-lamp, the bulging tumour behind the detached retina, the diagnosis is much easier.

In a case of angioma of the choroid beside the papilla—the diagnosis was made *after* enucleation—the retina in front of the tumour was very thickened and there was an extensive cystic degeneration. In view of the fact that in histological preparations of this disease an extensive cystic degeneration of the retina is almost always found in front of the tumour, the presence of an extensive cystoid degeneration in front of a tumour not at the macula may be of diagnostic value.

7. It seems to be of practical importance that in cases of choroiditis the retina is blurred and often slightly thickened in front of a focus of fresh inflammation (Fig. 11). Healed choroiditic scars are usually a little depressed, and the retina in front of them is of glass-like transparency. In old disseminated choroiditis (Fig. 12) it is sometimes very difficult to determine by means of the ophthalmoscope if there is fresh inflammation on the border of an old focus; slit-lamp examination enabled us to do so.

This short survey may show the diagnostic importance of slit-lamp microscopy of the fundus.

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BLOOD-VESSEL FORMATION IN THE CORNEA*

BY

F. W. CAMPBELL *and* I. C. MICHAELSON

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INTRODUCTION

THE experimental production of corneal vascularisation has been performed by various workers. Ehlers (1927) made daily applications of ethyl alcohol to rabbits' corneae resulting in a loss of corneal transparency and an ingrowth of vessels from all round the limbus into the anterior two-thirds of the cornea. Julianelle (1933) produced " pannus " formation by intra-corneal injection of proteins after sensitisation of rabbits and monkeys. Mann (1943) described new-vessel formation in the cornea after application of mustard gas and related substances. In none of these

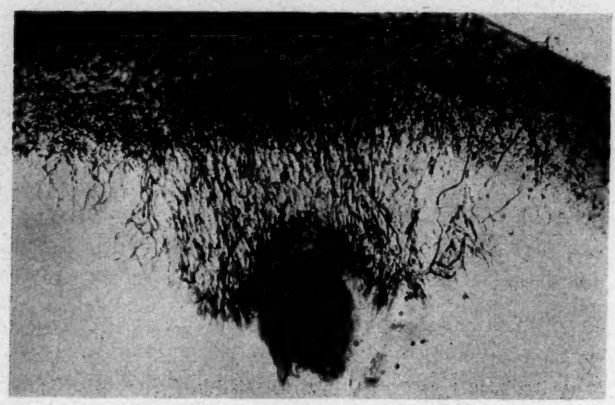

FIG. 1.

Note the isosceles triangular area of vascular infiltration from the limbal plexus above.

methods was the injury sufficiently localised or of an intensity constant enough for our purpose.

From clinical observation it is known that, if a localised lesion of the cornea is accompanied by vascularisation, the vessel formation usually begins at the part of the limbus nearest to the lesion, and that it often tends to take a triangular form as indicated in Fig. 1. We decided to study this phenomenon in rabbits under

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standard conditions unattainable in clinical work, and this series of experiments was designed to discover if the site of a localised injury such as a burn had any effect on the formation of these new vessels from the limbus.

METHOD

A " standard lesion " was produced by applying a platinum wire cautery to a rabbit's cornea for approximately two seconds. The cautery was kept at a uniform temperature throughout the experiment by supplying a constant voltage. Two minutes before cauterisation two drops of 1 per cent. pontocain hydrochloride

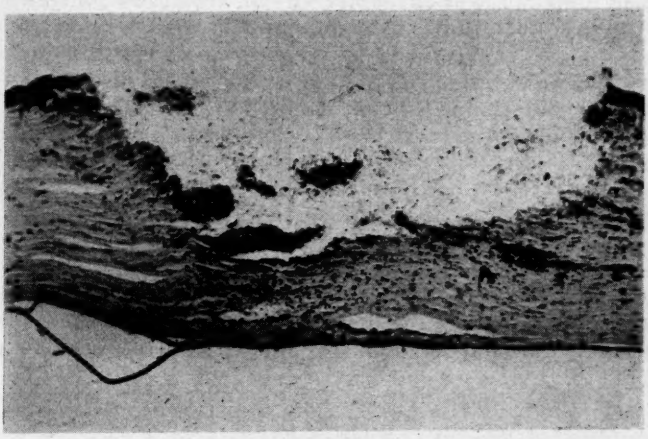

FIG. 2.

The lesion involves the epithelium and the anterior two-thirds of the stroma.

were placed in the conjunctival sac. The burn to each cornea was repeated daily on the same site for the duration of the experiment, usually 10-14 days. The lesion was about 1 mm. in diameter and involved the epithelium and the superficial two-thirds of the substantia propria (Fig. 2). With two exceptions infection of the wound did not occur. The distance of the injury from the limbus varied from rabbit to rabbit, although the injuries were placed along the same meridian—usually 12 o'clock.

At the end of the serial cauterisation the rabbit was anaesthetised with ether, a carotid artery exposed, and a cannula inserted directed cranially. Five to ten c.c. of a 50 per cent. dilution of Indian ink (Reeves) in water was then run in under a pressure of 100 to 150 mm. Hg until the vascularised area of the cornea was filled

with ink particles. The animal was killed, the eye excised and placed in 10 per cent. neutral formalin. For examination the whole corneal thickness, including the limbus, was mounted in glycerine. The vascularised area was measured with a microscope eyepiece-micrometer and with a Vernier moving stage.

RESULTS

Experiment 1. The right corneae of five young adult rabbits were cauterised daily for 13 days. In four of the corneae a typical triangular vascular area was produced. The results are presented in Table I. In these corneae, as in the others subsequently examined, the vascular triangle was isosceles (Fig. 1).

TABLE I

Rabbit	Distance of lesion from limbus in mm.	Size of isosceles sides in mm.
A	1·7	3·3
B	1·7	3·3
C	2·1	3·2
D	2·1	3·2
E	4·2	No vascularisation

In rabbits A and B with a lesion 1·7 mm. from the limbus, the length of " d " (Fig. 3) was the same—3·3 mm. That is, vessels grew from all parts of the limbus within 3·3 mm. of the centre of the lesion. Again, in rabbits C and D, with a lesion 2·1 mm.

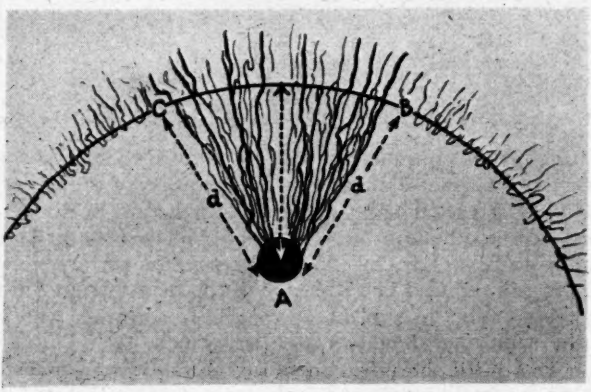

FIG. 3.

A diagramatic representation of the vascular triangle. The vessels do not all grow towards the lesion as shown, but tend to grow towards the centre of the cornea (Fig. 1).

from the limbus, vessels grew from all parts of the limbus within 3·1 mm. of the lesion. On the other hand, when the lesion was placed 4·2 mm. from the limbus as in rabbit E, the limbal vessels were not affected, and no vascularisation was produced.

The approximation of the measurements for " d " in these four corneae (3·3, 3·3, 3·1 and 3·1 mm.) stimulated us to repeat the experiment on a larger scale in order to investigate further the degree of constancy of " d " for a standard lesion.

Experiment 2. This experiment was carried out along similar lines, but both corneae were injured in each rabbit. In this group, only 10 successive daily cauterisations were done. Moreover the cautery point was larger and the temperature was slightly higher. The standard lesion, although constant within this group, was therefore different from that used in experiment 1.

The results in the second series of 8 rabbits involving 16 corneae are shown in Table II. Triangular areas of corneal vascularisation were obtained in all the eyes. The experiment on the left eye of rabbit G was spoiled by an error in the technique. In rabbit F the wounds became infected, as shown by general redness of the conjunctiva and a discharge from the eyes. All the other eyes were white and without discharge. We therefore excluded the results from these animals.

TABLE II

Rabbit	Eye	Distance of lesion from limbus in mm.	Size of isosceles sides " d " in mm.
A	Rt.	1·4	4·0
E	Lt.	1·9	4·4
C	Lt.	2·1	4·3
D	Lt.	2·1	4·4
H	Lt.	2·1	3·9
B	Rt.	2·2	4·4
D	Rt.	2·2	4·4
E	Rt.	2·2	4·2
A	Lt.	2·3	4·3
H	Rt.	2.4	3·8
G	Rt.	2·5	3·9
C	Rt.	2·7	4·2
B	Lt.	3·3	4·3

In the remaining 13 corneae the distance from the centre of the " standard lesion " to the basal angle of the vascular triangle is fairly constant. The mean of the measurement of " d " in these 13 corneae is 4·2 mm. with a standard deviation of 0·21 mm. The range is from 3·8 mm. to 4·4 mm.

In corneae H rt. and H lt. a triangle of pigment was noted to occupy the same position as the vascular area (Fig. 4). In the remaining rabbits limbal pigmentation was very slight or absent.

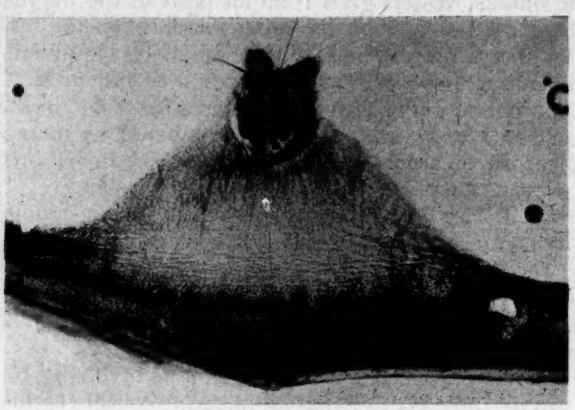

FIG. 4.

Note the migration of pigment from the limbal pigment ring below.

Experiment 3. Six rabbit corneae were injured under conditions identical with experiment 2. The " standard lesions " were made at 4·5, 4·6, 4·8, 5·0, 5·1, 5·3 mm. from the limbus. In no case was ingrowth of limbal vessels observed.

DISCUSSION

A localised lesion, in the rabbit's cornea, placed within a certain distance from the limbus, can produce an area of vascularisation which has the form of an isosceles triangle. If, however, the lesion is placed beyond this distance no vascularisation is observed. Further, there is a relatively constant distance between the site of the lesion and the basal angles of the vascular triangle (the distance " d " Fig. 3). These findings could be accounted for by assuming that a factor, which is produced by the corneal lesion at A (Fig. 3), diffuses from that situation equally in all directions, and in doing so becomes less effective the further away it is from A. The amount of this factor present at the angles B and C at the base of the vascular triangle would represent the minimum amount of the factor capable of stimulating limbal vessels to bud. Beyond B and C the concentration of the factor is apparently too low to stimulate budding.

The shape of the resulting vascular area can be readily appreciated by studying Fig. 5. Each large black circle represents a standard lesion, and the distance between the concentric lines is 1 mm. A factor diffusing from the lesion will become weaker,

the further it is from the source. Let us assume that, for this particular lesion, the factor is able to stimulate vascularisation up to the 3 mm. ring, while beyond this distance the factor is too weak to produce new vessels. It can be seen from Fig. 5 that, although the shape of the vascular triangle varies according to the distance of the lesion from the limbus, the distance from the lesion to the basal angles of the triangular area remains unchanged.

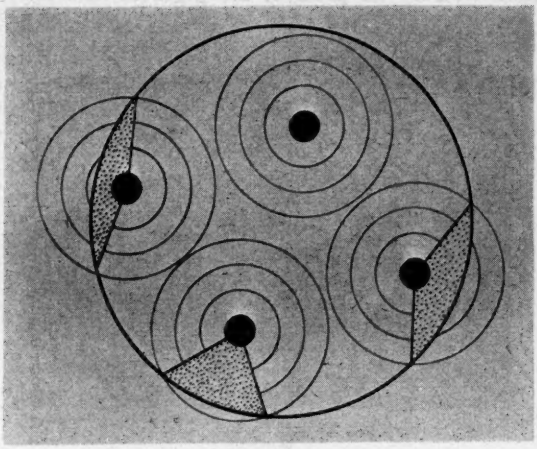

FIG. 5.

The black circle represents the standard lesion. The concentric lines are placed at 1mm. intervals. The shaded area indicates the theoretical shape of the area of infiltration.

The distance " d " (Fig. 3) is the radius of the zone in which the concentration of the " factor " is sufficient to produce vascularisation from the limbus.

The findings would then appear to offer evidence that new-vessel formation in the cornea, in the circumstances described, depends on a factor released by the primary lesion and diffusing from the site of the lesion.

Studies of the retina have also shown evidence of the presence in that tissue, in certain circumstances, of a factor or factors able to influence the budding of new vessels (Michaelson, 1948).

The nature of the factor liberated at the site of the burn might possibly be a substance similar to histamine directly affecting the limbal vessels. On the other hand there is evidence accumulating which suggests that there may be present in the normal corneae a

substance, or substances, which prevent the invasion of limbal vessels (Wise, 1943; Bacsich and Riddell, 1945; Bacsich and Wyburn, 1947). Destruction of this substance around the site of a thermal burn would allow new-vessel invasion of the cornea in a manner similar to our findings.

According to Mann (1944), pigmentation of corneal epithelium is evidence of healing by " sliding " of epithelial cells from the limbus on to the cornea. In the two corneae in our second series where pigmentation was present, the pigment was distributed in

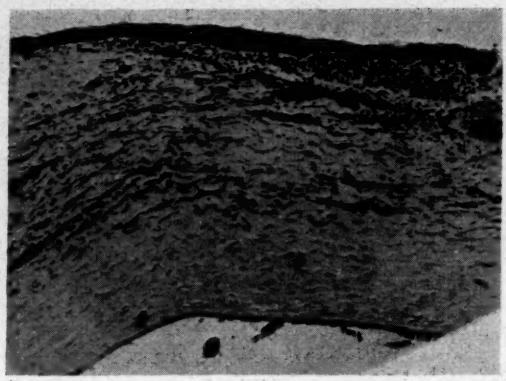

FIG. 6.

The epithelium is above. The vessels occupy the anterior two-thirds of the cornea. There is also considerable cellular infiltration.

a triangular form and co-extensive with the underlying new vessel formation. Furthermore, the vessels occupy the anterior half of the substantia propria and epithelium (Fig. 6). To us this raises the possibility that there may be a common mechanism influencing epithelial sliding and new-vessel formation.

This work has raised a number of interesting problems about the nature of the new-vessel stimulus, and it is hoped that further investigation will provide a clue to its structure.

SUMMARY

(1) A method is described for producing a relatively standard corneal lesion in rabbits and for studying the resulting vascularisation of the cornea.

(2) If the lesion is greater than a certain critical distance from the limbus no vascular response occurs. At less than this distance

from the limbus, vascularisation occurs, and the vascular area has the form of an isosceles triangle.

(3) If a series of "standard lesions" be placed at different distances from the limbus, but within the critical distance for that lesion, the distances between the sites of the lesions and the basal angles of the triangular vascular areas are fairly constant.

(4) The results suggest that the new-vessel formation in the cornea, in the circumstances described, involves a factor released by the lesion and diffusing from the site of that lesion.

We are indebted to Prof. R. C. Garry for helpful criticism and encouragement.

The cost of this investigation was defrayed by the Rankin Medical Research Fund.

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BOOK NOTICES

Principles and Practice of Ophthalmic Surgery. By E. B. SPAETH. Fourth edition. Pp. 1044. 8 colour plates, 649 figs. References in text. Henry Kimpton, London. 1948. Price, £3 15s. 0d.

This edition follows the lines of its predecessors, and like them will be warmly welcomed. In the writing of text-books on ophthalmic surgery, it is difficult to find the mean between, on the one hand, the author's personal practice, which is often so individualistic as to be of little value except to himself and those who are psychologically in relation to him, and, on the other, a compilation of the views of the many distinguished exponents of ophthalmic surgery as an art, a compilation which would be so compendious as to be useless and to appal even the stoutest-hearted bibliophile. The work under review has long been recognised to be as happy a compromise as may perhaps be expected in an imperfect part of the world where scientific doctrine and practice are as yet independent of the state, although, even in it, some may have considered that an undue amount of space has been devoted to the principles of plastic surgery and reconstruction; this criticism, however, is hardly valid in the aftermath of the war.

In the present volume the section on traumatic conditions has been amplified, and further material has been added in the sections dealing with paralytic squint and ptosis. Additions have also been made in the sections on exophthalmos and plastic surgery of the lids, while the section on enucleation has been rewritten to cover the recent work on plastic implants. Other minor additions have been made and the book has generally been brought up-to-date.

Refraction of the Eye. By A. COWAN. Third edition. Pp. 287. 187 figs. Bibliography. Henry Kimpton. London. 1948. Price, 27/6.

This book, in the opinion of the reviewer, is of considerably less value than many others which have been written on the subject. It follows the usual scheme of works of this nature; the first section deals with the physical optics of reflection and refraction, and while the mathematical exposition of the principles involved may be perfectly clear to those already familiar with the subject, one feels that the student preparing for an examination would be left somewhat bewildered, since the exposition hardly starts from first principles.

The succeeding chapters consider the eye as an optical instrument, and its ecological efficiency as such. A chapter on ametropia follows and one is, in the light of recent work, surprised to read that in myopia, in the absence of disease, it is safe to assume that the eye is anatomically too long. Nor will everyone agree with the author's views as to the importance of low-grade inflammation in the genesis of pathological myopia.

In discussing methods for the determination of refraction once again one feels that, as a practical guide, the chapter is of little value since, although much information is given, this is mainly suited to those who already have a considerable grasp of the theory and practice of the subject. The same criticism might perhaps apply to the succeeding section on the management and treatment of ametropia. The last chapter of the book gives a very elementary and short outline of the value of contact and telescopic lenses.

Altogether we feel that the book falls between two stools; its approach is not sufficiently elementary for the tyro, while, for the established refractionist, although it contains contentious passages which are always stimulating, it will do little to divert him from his established practice, however many heresies that practice may contain.

An Introduction to Clinical Orbitonometry. By A. C. COPPER. Pp. 125. 14 figs., 24 graphs. Stenfert Kroese (Leiden). Henry Kimpton, London. 1948.

The importance of estimating the resistance encountered in forcing the globe backwards into the orbit in the diagnosis of

orbital tumours was stressed by v. Graefe, but for over half-a-century such estimations depended on digital palpation alone. Langenhan was the first to devise an instrumental method of recording the orbital resistance (or tension); since his time three others have been suggested, but the orbitonometer devised by Copper has considerable advantages over them all. It consists of a dynamometer fixed to a supporting bridge which rests on the outer margins of the orbit and can be made to press the globe backwards by means of a plastic contact lens resting on the cornea and sclera. Readings of the displacement of the eye are then taken at intervals under increasing weights up to 400 gms. The instrument is suitable for general clinical use and is compact and easy to apply.

With this technique Copper has studied the retrobulbar resistance in 60 normal persons and has obtained a series of normal orbitonometry curves, their shape depending essentially on the volume of the retrobulbar space and the "orbital tension" which itself is composed of such factors as the tone of the extrinsic muscles, the amount of fluid which can be expressed from the orbit, and the consistency of the tissues. He has extended this study to pathological cases, particularly Graves' disease, exophthalmic ophthalmoplegia, acromegaly, intra-orbital inflammations, tumours and pseudotumours. In each of these diseases modifications of the normal curves are obtained. The resistance of the oedematous orbit of thyrotoxicosis can be differentiated from that of the infiltrated orbit of the exophthalmos not associated with hyperthyroidism, and space-taking lesions can be diagnosed before proptosis has developed. There is no doubt that, although the method cannot provide the differential diagnosis of a lesion such as a tumour, it is of great value in proving the presence of an abnormal density in the retrobulbar tissues, and providing objective information as to whether the process is progressive or stationary: the new instrument designed by Copper and the work he has done on its standardisation are advances in ophthalmological technique of considerable value.

Practical Orthoptics in the Treatment of Squint. By T. KEITH LYLE and SYLVIA JACKSON. Pp. xii and 251. 151 figs. Third edition. H. K. Lewis, London. 1949. Price 35/-.

Routine orthoptic supervision of children in Great Britain was curtailed from 1939 to 1946 by reason of transport difficulties, together with the absence of many orthoptists on war service. Nevertheless solid progress has been achieved during those years. Cases of ocular muscle imbalance occurring in the armed forces have been investigated and treated by new methods, many of which are applicable to children, although they could not readily have been evolved without preliminary trial among adult patients. Miss Billinghurst and Miss Salsbury appear to have made good use of

their Service experience, and each has been teaching and practising orthoptics for a number of years. Therefore Mr. Lyle is to be congratulated on having chosen worthy successors of Miss Jackson, the latter having now retired.

The format of this new edition, with its increased width of page, allows more scope for the larger illustrations, especially the Hess charts, and much important new material has been added. We predict a warm welcome for this amply-illustrated volume, which has been well printed on high-quality paper, and enclosed within dignified covers. A new edition of Practical Orthoptics was badly needed, not only because of the fresh methods of binocular stimulation devised since 1940, but also for the sake of stressing *differential* prognosis. Thus we read on pp. 34-35: "On no account should treatment be continued unless progress is being made . . . time should not be wasted giving orthoptic treatment to patients whose binocular anomalies are unlikely to benefit from such treatment. Every orthoptist should clearly understand the limitations of orthoptic treatment as well as its advantages."

Realism is the keynote of the work under review. The importance of preliminary investigation and accuracy of diagnosis are duly emphasised. The serious reader will soon notice that Mr. Lyle avoids facile generalisations, and is careful to illustrate his principles by actual case-records. Torticollis—a subject which has often been clouded by obscure descriptions in the past—is lucidly expounded, and the account of cases exhibiting abnormal head posture will repay detailed study. Mr. Lyle's wide experience in the refractive, orthoptic and operative treatment of squint and other anomalies of ocular muscle balance is backed by his constant awareness of the human problem. That is why he insists upon the need for encouragement and cheerfulness on the part of the orthoptist, with the object of strengthening the patient's will to be cured. Another great asset is Mr. Lyle's special knowledge of neuro-ophthalmology, which is evident on nearly every page. Practical Orthoptics is a distinguished piece of work, the influence of which will be enormous throughout and beyond the English-speaking world.

CORRESPONDENCE

GLIOMA OF THE RETINA

To the Editorial Committee of
THE BRITISH JOURNAL OF OPHTHALMOLOGY

DEAR SIRS,—I should be glad of the help that some of your readers may be able to give on this issue: To what extent is an

individual successfully treated for glioma of the retina liable to pass the affection on to his children?

That there is a hereditary factor in glioma of the retina is fully established. What is not known is whether all gliomata are hereditary. This could only be established if adequate information were available on the progeny of individuals successfully treated. There must be by now many patients who have reached adult life having lost one or both eyes in infancy (or retained an eye after successful radiotherapy). Some of these adults may have families, and it would be a great help to know whether any of their children have developed glioma. For a clear answer it is, of course, necessary to have information on children who are not affected as well as on children who are affected. If, as is assumed, glioma of the retina is dominant, 50 per cent. of the children of surviving patients should be affected unless modifying factors disturb the ratio.

In most dominant conditions tracing the family backward gives enough information. In the case of a highly lethal affection like glioma of the retina this procedure is not available. Moreover, there is good reason for believing that most cases of glioma represent new mutations rather than the continuance of a line of affected individuals.

I should be grateful if such of your readers who have the relevant information could let me have the following particulars:

(*a*) Name and a short personal history of the individual affected with glioma, and an indication, if available, as to the occurrence of glioma in relatives.

(*b*) The number (and, if possible, the sequence) of children in the second generation.

(*c*) Indication as to which, if any, of these children show glioma.

(*d*) In any glioma patients information as to whether the glioma was unilateral or bilateral would be appreciated.

Yours faithfully,

ARNOLD SORSBY.

ROYAL COLLEGE OF SURGEONS
LINCOLN'S INN FIELDS,
LONDON, W.C.2.
January 15, 1949.

To the Editorial Committee of
THE BRITISH JOURNAL OF OPHTHALMOLOGY

DEAR SIRS,—The infection of the conjunctival sac by larvae of flies (maggots) is relatively rare in Western Europe (Duke-Elder, Vol. II), and most of the cases recorded have been infections by the *hypoderma bovis.*

Whilst in Malta I obtained larvae specimens of *oestrus ovis* and submit the following case history:—

During July a Naval officer attended the Ophthalmic Department of the Royal Naval Hospital, Malta, complaining that following a swim in the sea the previous day something had entered his right eye, producing redness and irritation. Examination revealed three small worms crawling on the conjunctiva, each approximately 1·5 mm. long.

These were removed with forceps and the eye irrigated. In 48 hours the patient had recovered from the traumatic conjunctivitis.

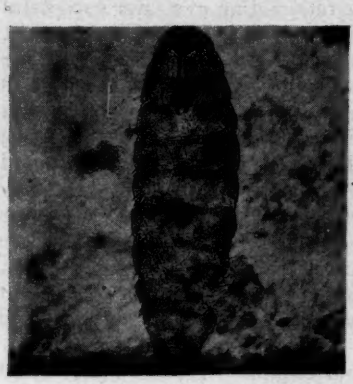

FIG. 1.

FIG. 2.

(During that period he used protargol drops 3 per cent.). No further attendances were necessary.

The specimens of the "worms" were mounted and have now been identified as larvae of *oestrus ovis*.

I am submitting two photographs of the larvae in case they should be of interest.

Yours faithfully,

GEORGE E. ROBINSON.
Surg. Lt.-Cdr. R.N.V.R.
Late Ophthalmic Specialist,
Royal Naval Hospital, Malta.

ROYAL INFIRMARY,
SHEFFIELD, 6,
December 2, 1948.

The ROYAL INSTITUTE of PUBLIC HEALTH & HYGIENE

Spring Session, 1949—Lectures to be delivered in
THE LECTURE HALL, 28, PORTLAND PLACE, W.1.

April 20 ... (1) "Occupational Eye Diseases and Injuries" (*Illustrated*)
April 27 ... (2) "Occupational Eye Diseases and Injuries" (*Illustrated*)
At 3.30 p.m. on each day.

Lecturer: Joseph Minton, F.R.C.S.
Chairman: Charles B. Goulden, O.B.E., M.A., M.C., M.D., F.R.C.S.

The next meeting of the Oxford Ophthalmological Congress will be held on July 7, 8 and 9, 1949, at Oxford.